THE Journal Kansas Medical Society

SEPTEMBER
1955
VOL LVI
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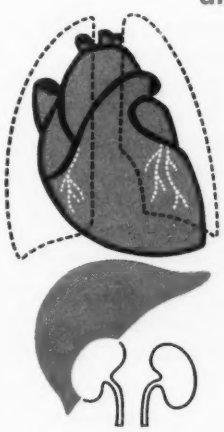

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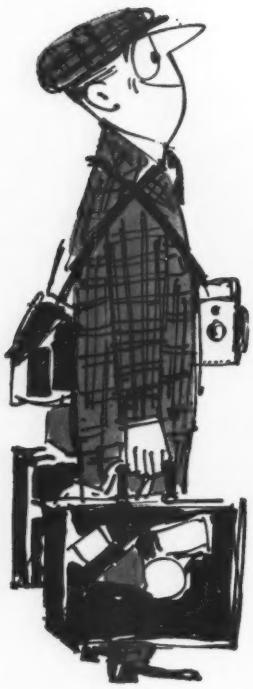

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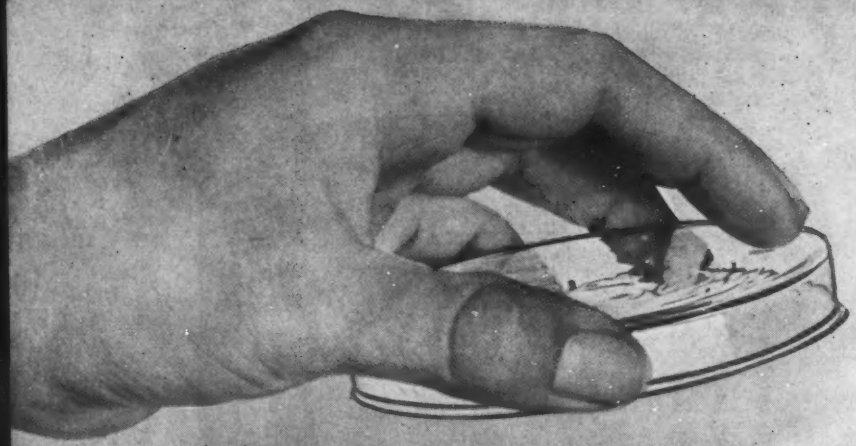

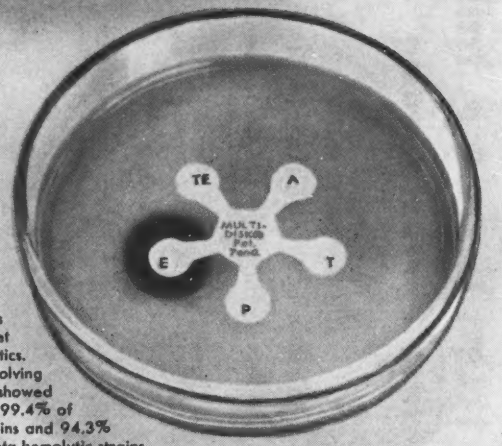

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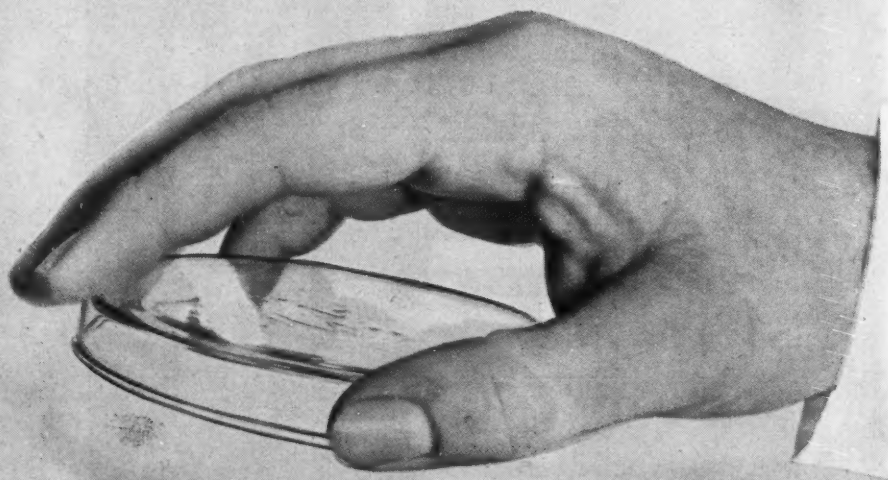

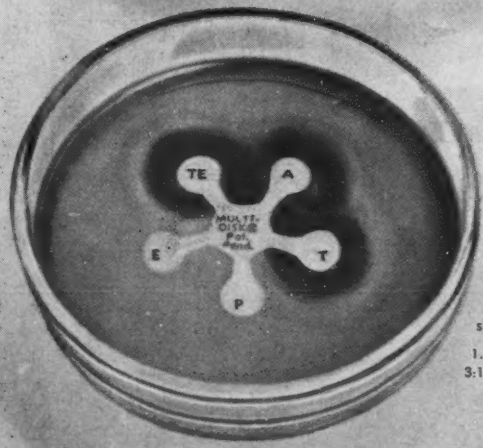

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1. Eisenberg, et al., Antib. & Chemo., 3:1026-1028, Oct., 1953.

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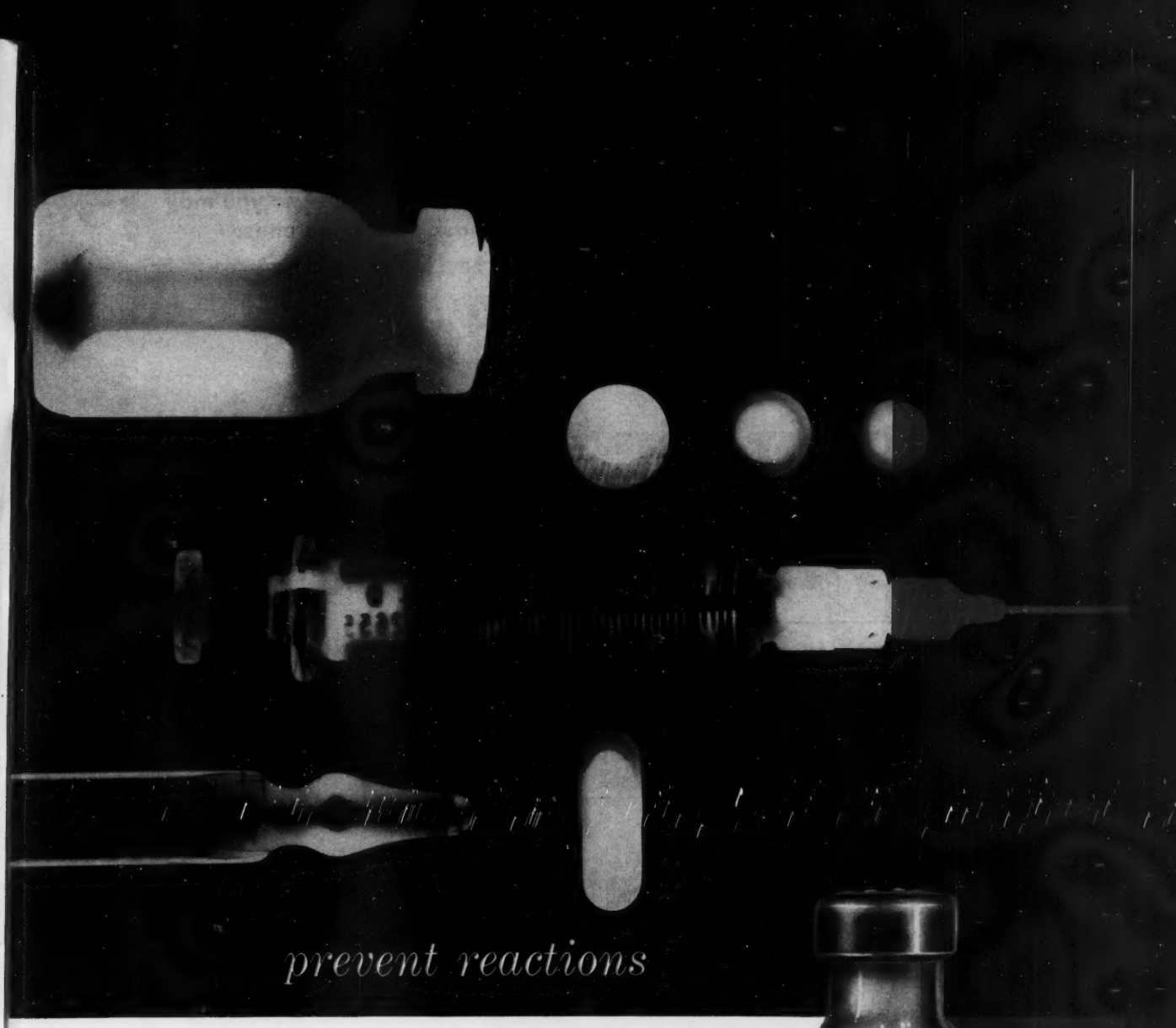

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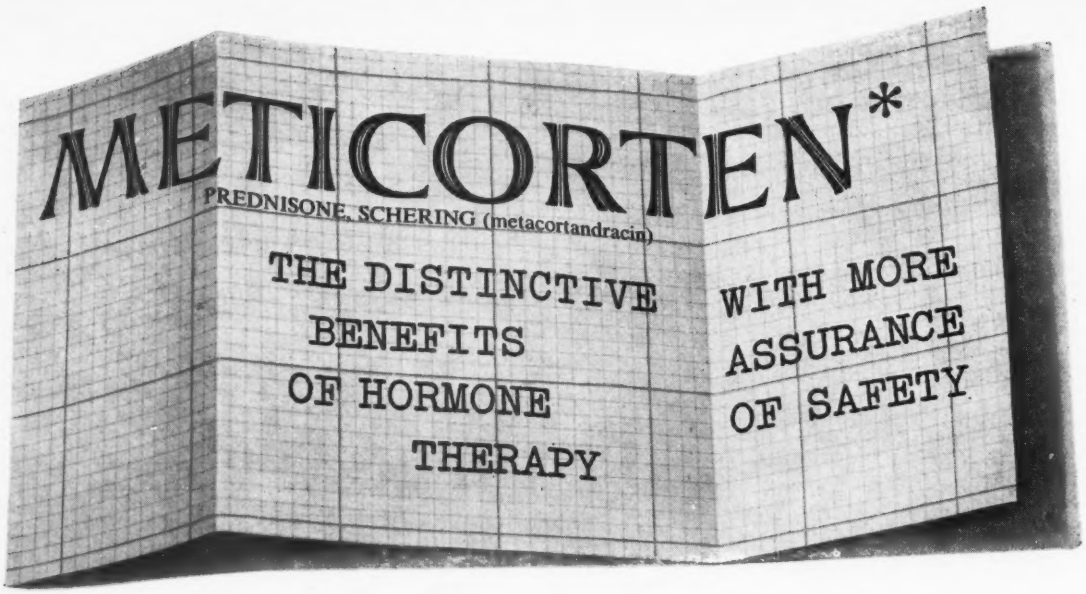

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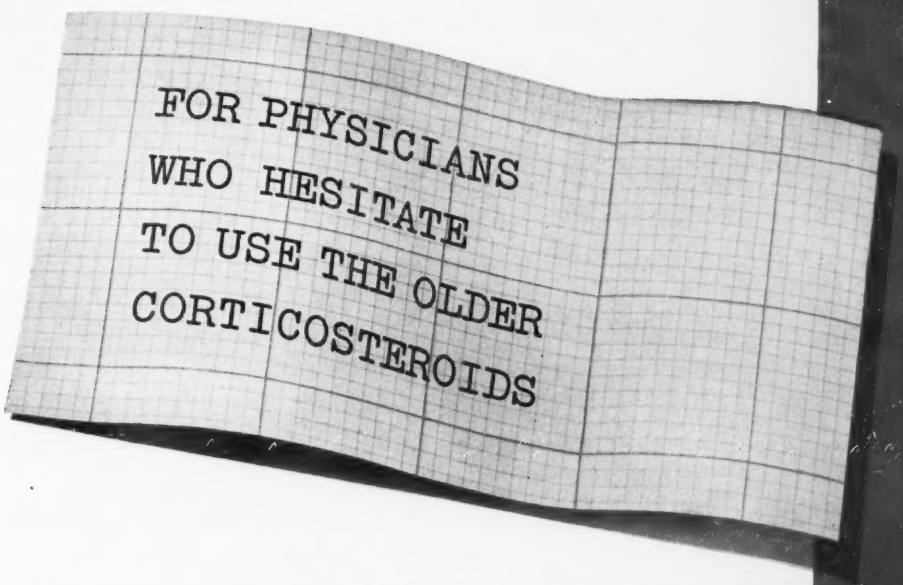

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Volume LVI SEPTEMBER, 1955 No. 9

Hypophysectomy in Metastatic Breast Carcinoma

Report of a Case

Philip W. Russell, M.D.
Wichita, Kansas

Currently, investigators in several medical centers are exploring the efficacy of hypophysectomy in metastatic breast carcinoma. This palliative procedure is an important step in clarifying theories of the hormonal-dependency of breast cancer. Therefore, further attention to hypophysectomy is warranted while it is still in the experimental phase of its development.

The use of hypophysectomy in patients with breast cancer was first described in this country by Olivecrona in November 1952.[1a] His recent report includes the results obtained by hypophysectomy in 37 patients with metastatic breast cancer.[1c] Hypophysectomy was incomplete in four patients, and three patients died of other diseases. Among 30 patients prior to June 1954, 13 patients survived from three to 28 months postoperatively. So far there have been few other preliminary reports of hypophysectomy for neoplastic disease.[2, 3, 4, 5] Olivecrona felt that among the various malignancies for which he performed hypophysectomy, those of the breast offered the widest field for its application. His one patient with malignant chorionepithelioma deserves particular notice, however, for apparently complete ablation of tumor cells was demonstrated following removal of the pituitary gland.

The investigative experience with hypophysectomy in the human being is much greater than published reports indicate at this time. For example, the group at Sloan-Kettering Institute is studying the effects of hypophysectomy in over 65 patients with breast carcinoma.[6] Their results have been relatively encouraging and have excited premature comment in the lay press. However, until complete statistics are reported, the latest recommendation of the Council on Pharmacy and Chemistry of the American Medical Association is that both adrenalectomy and hypophysectomy are experimental procedures that should not be employed in breast carcinoma generally.[7]

The following detailed case report is offered as a basis for discussion.

CASE REPORT

A 35-year-old premenopausal woman was first examined at Wesley Hospital on January 15, 1954. She had had a right radical mastectomy for duct cell carcinoma in January 1951. Skeletal metastases had been present since June 1953 and intracranial metastases since October 1953. She had received narcotics daily for one month. For two weeks she had been incapacitated with continual right trigeminal neuralgia.

Physical examination revealed left proptosis with weakness of the right fifth, seventh, eighth, and left sixth cranial nerves, with severe diplopia. A pea-sized mass was present in the left breast.

Roentgenologic skeletal survey disclosed areas of bone destruction in the thoracic spine, lumbar spine, pelvis, and ribs. One pathologic rib fracture was present. A roentgenogram of the chest showed slight bilateral pulmonary infiltration.

Testosterone cyclopentylpropionate, 50 mg., was

From the Department of Internal Medicine, Wichita Clinic.

injected three times weekly between January 15 and March 24, 1954. Roentgen therapy began with 1500 r to the right middle cranial fossa between January 19 and January 25. The final menstrual period ended January 15. Between February 1 and February 9, she received 2400 r to the mid-pelvis; no further menstrual bleeding occurred. The lumbar spine and pelvis were treated with 2700 r between February 25 and February 28.

Subjective improvement began January 24. By March 1, there was 75 per cent improvement in the right eighth and left sixth cranial nerve symptoms, with complete remission in the right trigeminal neuralgia and left proptosis. However, the left breast lesion increased in size to 3 cm. She was discharged from the hospital on March 6. At home she continued to receive nursing care, daily narcotics, and testosterone.

The second hospitalization began March 25. The patient was bedfast with recurrence of the trigeminal neuralgia. Striking progression was demonstrable in the skin, left breast, lymph nodes, lungs, pericardium, clavicles, scapulae, ribs, pelvis, and the entire spine. Three pathologic fractures were present in the ribs and pelvis. Because large doses of narcotics could not relieve the trigeminal neuralgia, an intracranial procedure seemed advisable. Hypophysectomy was elected by the patient and her family after all palliative procedures were explained. Testosterone was discontinued. Cortisone acetate, 75 mg. intramuscularly daily, was begun on March 26.

Hypophysectomy was performed on March 30, 1954, by Dr. A. H. Bacon and Dr. J. P. Schweinfurth. A right frontal osteoplastic craniotomy was used. As an illustration of the extent of the metastases in this patient, it was noted that the periosteum and most of the dura mater overlying the frontal lobe were infiltrated by tumor cells. Even the pituitary gland contained carcinoma. All gross pituitary tissue was removed.

Postoperatively, there was an impressive lack of morbidity. No changes requiring correction of blood pressure or electrolyte balance occurred. The patient was euphoric, comfortable, eating, and walking within 48 hours after surgery. As euphoria disappeared, subjective improvement increased rapidly during a three-week period and continued to increase for two or three months. Trigeminal neuralgia never recurred. Some sciatic pain persisted, requiring narcotics, to which preoperative addiction had been evident. Frequent coughing, which had been present preoperatively, disappeared in two weeks.

Diabetes insipidus began on the second postoperative day; its control was not necessary until the tenth day, when the daily urine volume was 14 L. No oliguric phase occurred. No hypoglycemia occurred. Serial serum potassium levels were normal. Neither calcium balance studies nor water excretion studies were done.

A 48-hour urine specimen collected April 24 showed absence of estrogen and gonadotropin.

Postoperative medical management depended on cortisone in divided doses of 75 to 100 mg. daily. During the first 60 hours, the patient received 5 L. of 10 per cent dextrose in distilled water, and 1 L. of 5 per cent dextrose in physiologic saline; thereafter no parenteral fluids were used. She received 4 grams of supplementary salt orally each day thereafter. Desiccated thyroid, ¼ grain, was given daily after April 13, although no evidence of myxedema was present at that time. Pitressin tannate in oil, 2.5 to 5 units, was injected regularly after April 10; attempts at withdrawal always induced excessive thirst and polyuria.

On discharge from the hospital May 8, 1954, the patient was remarkably self-sufficient. The duration of satisfactory regression was five and one-half months. Skeletal pain never disappeared entirely and required the use of narcotics; mild addiction remained. Nevertheless, for three months she did her own housework, cared for her pre-school child, and went shopping.

Objective improvement began with a change in cranial nerve signs two weeks after operation and was maximal during the fourth postoperative month. Objective improvement consisted of the following: (1) disappearance of five skin nodules, (2) a decrease in the left breast mass to one-fourth its original size, (3) decrease in lymphadenopathy, (4) disappearance of weakness of the left sixth and right seventh and eighth cranial nerves, (5) disappearance of proptosis, (6) weight gain of 28 pounds without edema, (7) obvious roentgenologic improvement in pulmonary infiltration, and (8) healing of the three pathologic fractures. Despite these changes, the existing bony metastases showed continual progression, and new osteolytic areas appeared.

The thyroidal uptake of radioactive iodine was 3 per cent on August 3.

On August 11, 1954, the patient was hospitalized for two days for definite acute adrenal insufficiency. This was caused by an attempt to lower the daily dose of cortisone below 62.5 mg. After 100 mg. of hydrocortisone intravenously, the previous maintenance dose of 62.5 mg. of cortisone proved sufficient.

On October 1, 1954, the patient developed intractable pain from a spinal cord lesion, and narcotic addiction became the major problem. Testosterone, 50 mg. three times weekly, was injected between September 20 and November 27, 1954. Roentgen therapy failed to give improvement. No cachexia was present. The patient expired on November 27, 1954, from pulmonary metastases.

Postmortem examination of the head was not permitted. All organs except the heart showed metastases from duct cell carcinoma. The thyroid gland was not removed. The adrenal glands, which contained metastases, showed atrophy and vacuolation of the zona fasciculata and zona reticularis. Fat stains demonstrated that these zones of the adrenal gland contained an increased amount of fat in small droplets.

COMMENT

Among several aspects of this case which deserve comment are: (1) the course of the patient prior to hypophysectomy, (2) the technic of operation and postoperative management, (3) the clinical evidence showing that hypophysectomy was complete. (4) the occurrence of diabetes insipidus, and (5) the appearance of the adrenal glands.

The preoperative treatment received by this patient consisted of roentgen therapy, roentgen castration, and testosterone. These were started practically simultaneously, as the patient was in a critical state. The initial control of trigeminal neuralgia was effected by roentgen therapy. The major preoperative remission, which began during the second week, started too soon to be attributed to androgen therapy. It was more characteristic of the response expected in 15 to 30 per cent of patients from castration.

It is of some interest that this patient had an apparent response to roentgen castration, as this implies that her tumor was of the so-called estrogen-dependent type at that particular time. The term "estrogen-dependent" is an arbitrary description applied to breast cancers in patients who exhibit any of the following: (1) response to premenopausal castration, (2) increased excretion of calcium following the administration of estrogens,[8] (3) significant urinary estrogen titers following castration, and (4) postmenopausal lactation following administration of luteotropin.[9] The concept of hormonal-dependency has been the chief rationale for the application of adrenalectomy to the problem of breast carcinoma. There is insufficient evidence in the literature at present to indicate that the routine determination of estrogen-dependency is of any importance in planning further treatment. More observations are needed. For example, Pearson[8] reported that among four patients who failed to respond to castration, none responded to adrenalectomy; among six patients who did respond to castration, five had some improvement after adrenalectomy.

Testosterone apparently caused progression of this patient's disease each time a course was given. The preoperative and postoperative courses of testosterone were of equal duration. Roentgenograms of the chest taken before each course showed the same degree of pulmonary infiltration, and those after each course of testosterone showed strikingly similar degrees of progression. Therefore, the suggestion is that the metabolic degradation products of testosterone, some of which may have estrogenic activity,[10] were unfavorable to this patient. The observation that this was true *before* and *after* hypophysectomy is important, for androgens produce partial repair of the adrenal atrophy produced by cortisone or hypophysectomy in rats.[11, 12]

The surgical approach in hypophysectomy involves sectioning one olfactory nerve.[13] A major problem in surgical technic arises from the fact that complete removal of pituitary tissue may be impossible, owing to the frequent presence of pituitary cells in the dural wall of the cavernous sinus. Evidence indicates that these cells can maintain partial pituitary function following hypophysectomy. In an effort to prevent failure of ablation from this source, the pituitary fossa is packed with cotton soaked in Zenker's solution for a few minutes before closure. Radioisotopes may be used in similar fashion.[14] In this patient, gross removal fortunately caused ablation.

Hypophysectomy in carcinoma of the breast is well tolerated. Operative mortality compares favorably with the 5 per cent mortality experienced in bilateral adrenalectomy. Postoperative morbidity was minimal in this patient. No more than the usual cerebral edema from craniotomy was noted with the preoperative and postoperative doses of cortisone and salt which were stated in the protocol. Cortisone, supplementary salt, desiccated thyroid, and pitressin if needed, prove sufficient for maintenance after hypophysectomy. In this patient, the minimum maintenance dose of cortisone was 62.5 mg. daily.

The criteria for complete hypophysectomy have been defined as follows:[15] (1) disappearance of urinary gonadotropin, (2) reduction of I^{131} uptake and serum protein-bound iodine to myxedematous levels, (3) acute adrenal crisis within one week after withdrawal of cortisone or ACTH, and (4) no evidence of pituitary tissue at autopsy. M. C. Li has reported that hypophysectomy was considered to be complete in 27 of 36 patients with neoplastic disease.[15] This patient exhibited all criteria except that protein-bound iodine determination and postmortem head examination were not performed. However, Li has stated that none of the patients fulfilling his first three criteria had pituitary tissue at autopsy;[6] furthermore, those patients who had abnormal thyroid studies after incomplete hypophysectomy regained normal indices within a few weeks.[4] Therefore, one may conclude that this patient had a complete hypophysectomy.

Sustained diabetes insipidus occurred in this patient. Diabetes insipidus may or may not occur after hypophysectomy. Postoperative polyuria usually oc-

curs, but its duration is unpredictable. The presence or absence of diabetes insipidus cannot be included among the criteria which indicate complete hypophysectomy. The exact role of the anterior pituitary in diuresis is not known. Much knowledge supports the opinion that diabetes insipidus is not sustained in the absence of a functioning adenohypophysis.[16] For example, patients with incomplete hypophysectomy are expected to have diabetes insipidus from pituitary stalk-section. However, 67 per cent of patients with complete hypophysectomy had clinical polyuria.[17] Furthermore, the persistence of polyuria in such patients after the third postoperative week depended on the continual administration of cortisone or ACTH.[1b] Recent evidence suggests, therefore, that polyuria following hypophysectomy does not depend on the presence of the anterior pituitary, and emphasizes the importance of ACTH as a mediator of the diuretic action of the adenohypophysis.

The adrenal glands of this patient exhibited definite atrophy, but the adrenal cortex contained abundant fat in small droplets. This was unexpected, as hypophysectomy causes adrenal cortical atrophy with depleted fat in large droplets.[18] The implication is that the adrenal pattern in this patient was altered by other factors. It is unlikely that cortisone alone produced the observed adrenal changes, for cortisone causes adrenal cortical fat depletion.[19] Testosterone can block the cortical fat-depleting effect of cortisone.[12] Histopathologic studies of the adrenal glands of hypophysectomized human beings, particularly those who have received cortisone and testosterone, have not been reported. In hypophysectomized rats, androgens with cortisone cause partial adrenal repair.[20] Perhaps testosterone caused a reappearance of fat in this patient's adrenal glands.

DISCUSSION

The newer methods of palliation in metastatic breast carcinoma include adrenalectomy, the use of cortisone alone, and hypophysectomy. Definite indications for the use of these methods have not been established as yet. They are not recommended as routine procedures. Considerable time must elapse before response rates and mean survival times can be accumulated.

Of these procedures, adrenalectomy has been the first attempted and most extensively used. Much experimental knowledge has been gained from its use. Bilateral adrenalectomy has a 5 per cent operative mortality rate[9] and is more traumatic than hypophysectomy. It must be remembered that bilateral adrenalectomy is not necessarily total, for 32 per cent of human beings have accessory adrenal cortices in the region of the celiac axis.[21] Objective improvement has occurred in 22 per cent, and subjective improvement in 45 per cent of patients in one series.[22] Any improvement may be evident within two weeks; the average response period is nine months.[23] The mean survival time following adrenalectomy has not been published.

The status of cortisone alone in the palliation of breast cancer is somewhat indefinite at present. It has been stated that cortisone is capable of producing such complete suppression of adrenal cortical function that adrenalectomy for neoplastic disease largely has been discarded.[24] However, similar case series are not available for comparison of adrenalectomy with the use of cortisone alone. Cortisone does cause reduction of urinary estrogen levels in postmenopausal women with breast cancer,[25] but not disappearance of estrogen with low doses. The few references in the literature to the use of cortisone alone report no objective benefit from ordinary doses. Pearson[26] believes that further trials with cortisone are indicated in doses of 200 to 300 mg. daily, with which he has estimated that 30 to 50 per cent of patients have objective improvement, and an additional 20 to 30 per cent have subjective improvement. The use of large doses of cortisone is justified only when artificial menopause, roentgen therapy, or proper hormonal therapy fail.

Hypophysectomy is more than another means of manipulating the hormonal environment. It is an important step in the experimental study of breast carcinoma. At present, the rationale for hypophysectomy is no more clear or well established than that for adrenalectomy. Like adrenalectomy, it is based in part on the hypothesis that certain hormones, particularly those having estrogenic activity, play a permissive role in the course of breast cancer. Therefore, one aim of hypophysectomy, not always accomplished, is the simultaneous suppression of estrogen sources in the ovaries, adrenal glands, and perhaps accessory adrenal cortices.

The use of hypophysectomy is based also on demonstrations in animal experiments that the pituitary gland plays a role in the development of breast cancer.[27] Its use in human beings may facilitate studying these mechanisms because of certain species differences in hormonal physiology. For example, Pearson[28] cites one patient in whom growth hormone stimulated a metastatic breast lesion. The patient had had a relapse after oophorectomy and adrenalectomy. Hypophysectomy was performed and regression lasted 14 months. Three months postoperatively, while the patient had an osteolytic lesion and was receiving cortisone, growth hormone was injected daily. This caused a rise in calcium excretion, with a negative calcium and phosphate balance in the same proportion as these ions exist in bone. The calcium

excretion returned to normal promptly on withdrawal of growth hormone.

SUMMARY

A patient with metastatic duct cell carcinoma of the breast had excellent objective and subjective improvement for five and one-half months after hypophysectomy. Postoperative survival time was eight months. Osteolytic lesions did not regress. Testosterone caused progression of disease before and after hypophysectomy.

Hypophysectomy should not be established as a palliative procedure for metastatic breast carcinoma until statistics demonstrate that the results offered will justify the means employed.

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People seem to resent the American Medical Association as being to blame, in some vague way, for sickness that has created a problem for them.

As a matter of fact, people actually resent illness. Illness is not planned for. It disrupts the routine of life. It is unpleasant. It is dangerous and threatens to kill those we love. It is expensive.

We must in some way get people to realize that really the American Medical Association is in their corner in this great fight for health.

Vincent Askey, M.D., Vice-Speaker
A.M.A. House of Delegates

The Treatment of Pulmonary Emphysema

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In order for us better to understand the treatment of pulmonary emphysema it might be well to discuss briefly the various types of this disease as we understand it today. The classification is somewhat confusing though much has been written on the subject.

The word "emphysema" comes from the Greek and means "inflation." Pulmonary emphysema was first described by Floyer of Litchfield in 1698, who called this condition "flatulent asthma" by which he meant that the lungs were blown up with air. Laënnec in 1838 and Jenner in 1857 gave us a better understanding of the clinical and pathological aspects of this disease. It may be localized or diffuse, acute or chronic, unilateral or bilateral, and it is characterized by loss of elasticity and dilatation of the pulmonary alveoli, with eventual rupture of the walls of the alveoli and the formation of inelastic blebs or bullae.

We may further classify pulmonary emphysema as: (1) compensatory emphysema, (2) acute vesicular emphysema or bullous emphysema, (3) senile, atrophic, or nonobstructive emphysema, and (4) pseudohypertrophic emphysema or so-called hypertrophic emphysema, chronic pulmonary emphysema, or obstructive emphysema. This latter form has at least nine other adjectives of which perhaps the most descriptive is the term "chronic large lung."

Compensatory emphysema of the acute form, which is reversible, may be seen associated with such diseases as bronchopneumonia, lobar pneumonia, and tuberculosis. It is a nonobstructive distention of a part or of the whole lung and may be associated with a shift of the mediastinum. However, if fibrosis occurs, the disease becomes chronic or permanent and is irreversible. Compensatory or localized emphysema may also be due to destruction, maldevelopment, or surgical resection of adjoining segments of lung or resection of the opposite lung.

The treatment of the acute form of compensatory emphysema would be that of the underlying or causative disease. In the case of thoracic surgery, preoperative determination of the condition of the uninvolved lung is most important. The operation may be a success, but the patient may have such poor function of his remaining lung that he is worse off than before his operation. Secondary thoracoplasty may be necessary to eliminate dead air space and thus prevent extensive degrees of compensatory emphysema in the opposite remaining lung.

Acute vesicular or bullous emphysema is a condition which may occur rapidly in cardiac dyspnea. It is seen as a serious and even fatal complication in children with asphyxia due to obstruction of the bronchi and bronchioles, associated with whooping cough, acute tracheobronchitis, influenza, measles, and bronchopneumonia. It also may occur following the aspiration of a foreign body, or with asthma, bronchogenic carcinoma, pneumonoconiosis, and sarcoidosis. In other words, this condition can occur with any disease which involves one or more portions of the bronchial tree. Bullae may become very large and are then known as balloon cysts or pneumocysts and may be mistaken for pneumothorax.

Alarcon reports in the January, 1955, issue of *Diseases of the Chest,* the appearance of large multiple bullae in the parenchyma of one or both lungs, which tend to grow or to decrease and eventually disappear. These bullae are seen in tuberculous patients receiving antibiotics or chemotherapy, particularly in those receiving isoniazid. He also says that this phenomenon has been reported to have occurred in patients treated with streptomycin and para-aminosalicylic acid. Only 25 such cases have been reported in Europe and South America, while one such case has been reported in the United States. The mechanism of the development of these bullous cavities has not as yet been satisfactorily explained. The outcome has been favorable, with rapid improvement of the general condition, gain in weight, the disappearance of toxic symptoms, and eventual disappearance of the bullae.

Bullae in nontuberculous patients, in cases where the cyst is solitary or where there is a collection of cysts in one portion of the lung, may be removed surgically, but widespread cysts are best treated the same as chronic emphysema.

We will next consider senile emphysema which is also called "atrophic" or "postural" emphysema. This is a nonobstructive form of pulmonary overdistention, a condition where the lungs are small. At autopsy, when the chest is opened, the lungs collapse. Alveoli are found dilated, and they lack elasticity, just as does the skin of old people, and may be likened to degenerative changes seen in all tissues of an elderly person. There is lack of muscle tone of the chest wall, the costochondral and costovertebral junctions are found to be calcified, the bronchi may show calcification, the pulmonary vessels are sclerotic, and there are myocardial changes com-

mensurate with old age, leading to pulmonary congestion and finally cardiac decompensation.

There is another form of senile emphysema which is known as the Kountz-Alexander type. Lung changes are secondary to an increase in the size of the thoracic cage, brought about by a degenerative process in the intervertebral discs causing the spine to become straight and stiff. As the degeneration progresses, the intervertebral discs become separated from the vertebra and may even disappear entirely. This leads to kyphosis and an outward flare of ribs, which in turn produces barrel chest. The lungs follow the enlargement of the chest cavity and therefore increase in volume.

Since cardiovascular disease is the common cause of dyspnea in emphysema of old age, we direct our treatment to this condition. Digitalis and mercurials are used, and when bronchial infection complicates the picture, we combat this by the administration of the proper antibiotic. We deem this more important than trying to treat the emphysema itself.

Treatment of emphysema of the aged is otherwise much the same as in hypertrophic emphysema. Vital capacity is somewhat reduced in senile emphysema, but there is usually little impairment of the respiration function in uncomplicated cases.

The so-called hypertrophic emphysema is better termed "pseudohypertrophic" emphysema because there actually is no increase in cellular or tissue structure, but rather a destruction of alveoli and loss of elastic fibers. With the development of emphysema, many of the interalveolar septa are destroyed, creating cyst-like air spaces in the lungs. Those localized in the subpleural portion of the lungs are called blebs, while those in other parts of the lungs are known as bullae. There is also a decrease in the corresponding pulmonary capillary bed.

This type of emphysema affects both lungs, and in children it usually follows recurring attacks of asthma or bronchitis with diseased tonsils and adenoids. It may also follow whooping cough. In older patients, mostly men, it may occur secondary to such conditions as bronchial asthma, chronic bronchitis, and any pulmonary condition where there is partial bronchial obstruction. Inhalation of harmful dusts, fumes, and gases over a prolonged period may cause emphysema. Hereditary emphysema has also been described, and we know that emphysema may occur in several members of the same family. Cohnheim and Eppinger believe this is due to a developmental defect of elastic fibers.

The tracheobronchial airways are elongated and dilated during inspiration, because they take part in the general expansion of the lungs as the thorax enlarges, and they return toward the resting state on expiration when the chest becomes smaller. Inspiration may not be affected significantly by partial obstruction, but expiration may be greatly affected. The alveoli do not empty normally; there is stretching and narrowing of the alveolar capillaries. There are progressive trophic changes, with loss of elastic tissue and rupture of interalveolar septa with the formation of blebs and bullae. These do not empty as completely as normal alveoli; the elastic recoil of the lung is diminished, and as more air is trapped with each succeeding breath, the lungs slowly increase in size.

The chest cage tends to assume the inspiratory position and appears to be fixed and inflexible. The diaphragm is flat or low, having a stretched appearance. Negative intrapleural pressure approaches zero, but with increased respiratory effort there is a wide swing, positive in expiration and negative in inspiration. The vital capacity (the maximal volume of air that can be expelled from the lungs by forceful effort following a maximal inspiration) is diminished. The tidal air (the volume of air moving in and out with each breath during rest) is normal or little impaired, while the residual air (that remaining in the lungs in extreme expiratory position) increases. The minute volume of respiration is also increased. The oxygen saturation of arterial blood is reduced from 95 per cent (normal) to less than 90 per cent, even at rest. This is due to unequal mixing and distribution of inspired air with residual air in the enlarged alveoli. At the same time there is an increase in the CO_2 tension in both arterial and venous blood. As the disease progresses, this eventually causes a severe respiratory acidosis. With the progressive anoxia, a compensatory polycythemia usually develops.

At first there may be little strain upon the right ventricle because of reduced capillary bed, but with advanced pulmonary emphysema, pulmonary arterial hypertension frequently develops. There is an increased strain on the right side of the heart which eventually causes right-sided heart failure, and cor pulmonale.

The symptoms of hypertrophic or pseudohypertrophic emphysema come on insidiously. There is usually a history of asthma or chronic bronchitis or of prolonged exposure of certain silica or asbestos dusts. Dyspnea occurs on slight exertion, often with expiratory wheezing. Cyanosis is observed, and there is an increase in venous pressure which can be seen by the fullness of the jugular veins and even the arm veins. Most patients have some degree of cough. There is easy fatigue, poor appetite, and insomnia. Pain in the epigastrium may occur and is due to overstrain of the abdominal muscles, or may result from heart failure with an enlarged liver or anoxia of the diaphragm. The accessory muscles of respiration are

active, and there is marked increase in the time of the expiratory phase. The anteroposterior diameter of the chest is increased with an elevation and horizontal position of the ribs, producing the characteristic "barrel chest." Chest expansion is reduced and protrusion of the upper abdomen is less pronounced or even absent.

The physical signs are rapid, shallow breathing with the chest held in permanent inspiration position. The apex beat of the heart cannot be seen or palpated. Heart sounds are distant. Tactile fremitus is diminished throughout. The percussion note is hyperresonant and even tympanitic, sometimes even including the cardiac area. Breath sounds are feeble with short, faint, harsh inspiration and prolonged low-pitched expiration. Sibilant and sonorous rales are often heard.

X-rays of the chest show enlarged lung fields which are highly illuminated, with the upper lobes showing a decrease in density while the lower lobes may show an increase in density. When bullae are present, they will be seen as fine lines in the shape of crescents, semicircles, and even complete circles. The diaphragm is low with a decrease in its convexity. The ribs appear more horizontal with a widening of the intercostal spaces. The anterior and posterior mediastinal spaces are enlarged. Kyphosis of the dorsal spine is seen. The heart shadow is usually small.

In the treatment of pseudohypertrophic emphysema we must first consider preventive measures. Diseased tonsils and adenoids in youngsters should be removed. Often allergic manifestations make themselves known early in life. There is usually a family history of allergy or asthma, and in these patients the control of the allergic condition offers the most important indication for treatment. Great care must be exercised to help prevent recurring attacks of bronchitis.

We advise patients to live in a warm equitable climate during the late fall and winter months, and they should remain there until well into the spring months. This, however, is seldom possible, so we advise our patients to wear warm clothing of a nature that will prevent perspiring indoors and chilling out of doors. Sudden changes in temperature, such as going from overheated homes and places of work out into the cold, are particularly bad. We advise our emphysematous patients to wear a two-fold underwear consisting of a pure cotton inner layer and 25 per cent wool outer layer. Woolen sox should be worn because wool does not chill when wet as does cotton. Smoking should be prohibited.

We advise our patients as to their activities and restrict these to whatever they can do without fatigue. Some activity is advised as this helps to prevent mental depression. Since many emphysematous patients are obese, a reduction in weight is necessary to reduce the demands upon both circulation and respiration. Conversely, when there is weight loss due to anorexia, we prescribe appetizers and vitamins.

Bronchial infection such as chronic bronchitis is often associated with chronic emphysema. Paroxysmal coughing and wheezing, with sputum, tend to aggravate the bronchiolar obstruction by exudate and edema of mucous membranes. Repeated upper respiratory infections during the winter months are common in these patients. Bronchiectasis is a rather frequent complication of chronic bronchitis and emphysema. Effective and appropriate antibiotic therapy must be instituted immediately. Organisms from the nose, throat and sputum should be identified, and sensitivity tests of the bacteria to the various antibiotics should be made. In cases where therapy is prolonged, one must be on the alert for a change in bacterial flora. Reinfections due to these new invaders, as bacteria, molds, and fungi, may be serious.

Penicillin is given if the organism is predominantly gram-positive, and streptomycin is added or given alone when gram-negative organisms are also present. Antibiotic aerosols combined with bronchodilator substances are used, but we hesitate to do so because of the hazard of local or generalized allergic reaction to penicillin and streptomycin. Antihistamine preparations may be given, orally or parenterally, to minimize these reactions. Broad spectrum antibiotics such as aureomycin, achromycin, and terramycin may also be employed. We have never felt that antibiotic aerosols would or could reach poorly ventilated lung areas properly and feel that the parenteral route is best. In cases where penicillin fails to get into the sputum in high enough concentration, Neo-Penil, a hydriodide ester of penicillin, given intramuscularly in doses of 500,000 units every eight hours, will produce a low systemic blood level with a high sputum concentration.

Bronchiolar obstruction due to conditions other than infection are treated with bronchodilator drugs. There are many antihistaminic preparations on the market, but we prefer to use an equal mixture of syrup of hydriodic acid and orthoxine hydrochloride, one teaspoonful four times daily after meals and at bedtime. In addition to this we use Cardalin, a protected aminophylline preparation. Each tablet contains aminophylline 5.0 gr., aluminum hydroxide 2.5 gr., and ethyl aminobenzoate 0.5 gr.

The low incidence of gastric disturbance with this preparation is noteworthy, and higher and more sustained theophylline blood levels are obtained, thus giving more continued relief from paroxysms of bronchiospasm with increase of vital

capacity and decreasing dyspnea and orthopnea. Of the aerosol bronchodilators, Isuprel seems to be the best sympathomimetic drug. We have our patients use this in a nebulizer, either alone or with Alevaire. The patient should be instructed carefully how to use these to best advantage. He is advised to exhale completely, then inhale deeply as he vaporizes the solution by compressing the bulb of the nebulizer. This should be repeated three to six times, and patients are often advised to use this before meals and at bedtime. Aerosols are also introduced with oxygen as the source of pressure, but there must be no water in the humidifier. Neosynephrine hydrochloride is also a useful preparation where refractoriness or toxicity has occurred from the use of bronchodilators. It likewise helps to diminish vascular engorgement of the pulmonary vascular tree.

Oxygen inhalation in the treatment of chronic emphysema is primarily for the relief of anoxia that occurs during various stages. Inhalation of oxygen in low concentration is the safest to use, and oxygen may be administered by nasal catheter, face mask, face tent, or enclosed tent a half to one hour two or three times a day. In cases of severe dyspnea or anoxia, continuous oxygen may be given with caution.

The syndrome of carbon dioxide intoxication and respiratory acidosis may occur in patients receiving oxygen. High concentrations of oxygen given suddenly are poorly tolerated, causing such symptoms as headache, weakness, confusion, lassitude and irritability, due to cerebral effects secondary to high CO_2 and a depression of pH, followed by depression of respiration, coma, and sometimes death.

Encouraging results have been reported after the use of intermittent positive pressure breathing in the treatment of pulmonary emphysema. Trimble and Kieran report that approximately two-thirds of a series of 37 patients experienced substantial improvement. They used 100 per cent oxygen inhaled through a Bennett valve, type TV-2P, which allows the oxygen to flow into the lungs under regulated inspiratory pressure of up to 20 cm. of water. Isuprel was nebulized into the oxygen stream in most of their patients. Improvement was noted in the three most outstanding symptoms: dyspnea, cough, and sputum.

Pneumoperitoneum therapy is considered by a number of clinicians as an effective procedure to help restore a more efficient function of the diaphragm. For many emphysematous patients, the diaphragm is the only structure capable of carrying on pulmonary ventilation. The diaphragm is elevated by the increased intra-abdominal pressure which helps to re-establish the normal pressure differential between the two sides of the diaphragm. With the return of negative intrapleural pressure, there is return of its normal pulling action on the diaphragm with a resultant improvement of pulmonary ventilation.

Satisfactory results will not occur in the presence of extensive pulmonary fibrosis, adhesions, or atrophy of the diaphragm or when the lungs have lost all of their elasticity. In these cases the lungs become compressed, blood accumulates in the right ventricle, cardiac output is decreased, and circulation time is increased, which leads to eventual heart failure. Beck, Eastlock, and Barach recommend venous pressure as a guide for pneumoperitoneum therapy. They advised that the treatment be discontinued if there is a rise in venous pressure, but it is a good sign if it shows no change or drops.

Breathing exercises should be taught all emphysematous patients. Schutz in 1935 was the first to recommend expiratory breathing with pursed lips. Active and passive diaphragmatic breathing exercises have long been found valuable. Manual compression of the upper abdomen and lower chest, in rhythm to the expiratory phase of respiration, is useful when the procedure is faithfully practiced daily. Specially constructed abdominal belts which raise the diaphragm by pressure from below are often beneficial.

Chronic cor pulmonale with or without congestive heart failure usually manifests itself in the final stages of chronic emphysema. Digitalis should be used when there is evidence of right ventricular failure. Mercurial diuretics are used in patients with cor pulmonale, even though there may not be definite cardiac failure. Diuresis diminishes extracellular body fluid. Frequent small doses of mercurial diuretics are preferred to large doses, because the latter may lead to sudden loss of electrolytes. Patients should be weighed daily so that their weight loss can be regulated. A weight loss of two to four pounds after a mercurial injection is preferred to greater loss. Eventually the patient should be maintained at or as near to his "dry" weight as possible.

Heavy sedation should be avoided as both barbiturates and morphine depress the respiratory center. Sodium bromide, chloral hydrate, and paraldehyde may be used. These can be given rectally in olive oil or cornstarch emulsion. When heavy sedation is required, ether is used, 60 to 90 cc. in an equal amount of sweet oil high up in the rectum.

In cases of chronic pulmonary emphysema secondary to bronchial asthma that do not respond to treatment as already outlined, we use ACTH, cortisone, hydrocortone or Meticorten. Effective relief from symptoms may be provided from these preparations when all other known measures of therapy have failed. Hydrocortone has been found to bring about improvement in one-half the dosage of cor-

tisone, with easing of symptoms noted on the first or second day of treatment. The dosage of Meticorten is from one-fourth to one-fifth that of hydrocortone, and the advantage of this steroid is that it is devoid of the major undesirable actions of sodium retention and excessive potassium depletion.

Contraindication to any of the steroids would be peptic ulcer and active pulmonary tuberculosis. In patients with inactive tuberculosis, it is advisable to use streptomycin and para-amino salicylic acid therapy.

SUMMARY

1. Pulmonary emphysema of various types has been classified as to: localized or diffuse, acute or chronic, unilateral or bilateral, and as (1) compensatory, (2) acute vesicular or bullous, (3) senile, atrophic, or nonobstructive, and (4) pseudohypertrophic or hypertrophic, chronic pulmonary emphysema, or as obstructive emphysema.

2. Pathologic and clinical aspects have been briefly discussed, together with treatment.

3. Pulmonary emphysema is common, and chronic forms are usually irreversible.

4. As our population grows older, we are finding more patients with pulmonary insufficiency, making them "pulmonary cripples."

5. Treatment of these patients depends on a well planned, individually outlined program which necessitates the cooperation of the patient.

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Lymphoepithelioma of the Parotid Gland

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INTRODUCTION

Literature referable to parotid tumors is most confusing. Many tumors have not been recognized as a definite entity and have been reclassified under another name. It is our purpose to present here an example of a rare benign lesion of the parotid gland.

In 1951, Kirklin[4] stated the basic concept when he voiced the opinion that the difficulty was inherent in the classification of these lesions themselves. Kirklin *et al.* presented a good classification in which the lymphocytic tumors of the parotid gland are listed in category six, comprising 1.5 per cent of all neoplastic lesions of the gland. We believe this tumor falls in this group.

These tumors have been occasionally called Mikulicz's syndrome or Mikulicz's disease in the past. Tumors of the parotid bearing the name of Mikulicz fail to follow any consistent, pathologic structure. To attempt to delineate this group is impossible. Kirklin *et al.* failed to find a description of these tumors in the literature prior to 1951. These tumors were char-

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acteristically described as consisting of a monotonous array of lymphocytes with an occasional germinal center and areas of reticulum cells.

In 1940, Fein[1] presented one case which he called "lymphoepithelioma." Fein mentioned a tumor described by Regaud[7] in 1912. Extreme radiosensitivity was mentioned by both Fein[1] and Regaud.[7]

In 1952, Godwin[3] reported 11 cases which he labeled variously as "adenolymphoma," "chronic inflammation," "lympho-epithelioma," "lymphocytic tumor" and "Mikulicz disease." In one instance comparison with the series reported by Kirklin[4] was made by McDonald,[4] by actual pathologic examination. These tumors were found to be identical with the lymphocytic tumor reported by Kirklin.[4]

The lesions described by Godwin[3] consisted of lymphocytic tissue containing germinal centers which appear to originate in the ductal tissue of the gland.

All recent authors suggest that these lesions are not malignant in nature. Also mention is made of their susceptibility to radiation.

Nash and Morrison[6] described a bilateral swelling of the parotid of a lymph-epithelial nature in a 27-year-old female, which responded to esophageal gastroplasty of the Finney type. It was felt that local manifestations were indicative of a generalized disease.

Lynch and Sucre[5] reported, in 1955, a single case in a 41-year-old male. The mass in one parotid gland was thought by the authors to be malignant and to represent a reticulum cell variant of the lymphoma group. It was felt that this represented a malignant variation of the tumor described by Kirklin[4] and associates. This seems to further emphasize the difficulty found in the classification of these tumors.

This type of tumor has been mentioned in the same breath with papillary cystadenoma, lymphomatosa, adenolymphoma, papillary adenolymphoma, papillary cystadenoma, branchiogenic cystadenolymphoma, branchiogenic adenoma, cylindrocellular branchiogenic adenoma, onkocytoma, and Warthin's tumor. Gaston and Tedeschi[2] have considered all these in the same classification and category. It is not felt that the lymphocytic tumors should be mentioned as identical with the adenolymphoma.

CASE REPORT

Mr. J. A. S., farmer, age 21, presented himself in 1951 with a discoid lupus erythematosus; biopsy was done, and on conservative treatment the lesion disappeared.

The patient next presented himself in 1954, at which time he complained of a bilateral parotid swelling. The patient had noted this swelling more on the right than on the left for approximately one year. It was painless.

Physical examination revealed normal findings with the exception of a bilateral swelling approximately 3½ x 4½ cm. in the right parotid area and a mass approximately 1 x 3 cm. in the left parotid area.

Sialograms were done on March 30, 1954. There was no evidence of ductal obstruction.

The material removed from each side was identical in appearance and consisted of white, somewhat friable tissue without any striking gross features.

Microscopic examination showed masses of lymphocytes, throughout which were solid areas of epithelial cells (Figure 1). Both the lymphocytes (Figure 2) and the epithelial cells (Figure 3) were mature. It was thought that this lesion represented one of the so-called "benign lymphoepithelial" lesions of the salivary glands, and it was so diagnosed.

Sections of the characteristic pathologic tissue and the slides were sent to Dr. D. C. Dahlin, Department of Pathology, St. Mary's Hospital, Rochester, Minnesota. It was his opinion that this was a benign lymphoepithelial lesion and that it would fall into the sixth category described by Kirklin[4] in his classification.

The patient received 900 roentgens of x-ray therapy applied to each parotid. The patient experienced a melting away of the growths in question. X-radiation resulted in a cure of the lesion. This particular

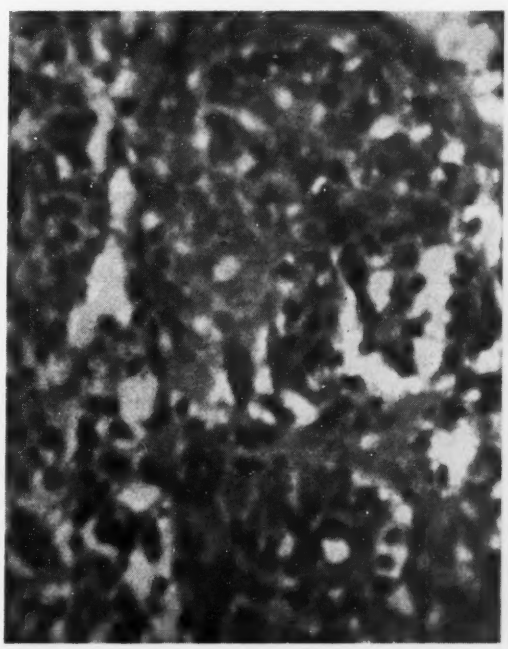

Figure 1

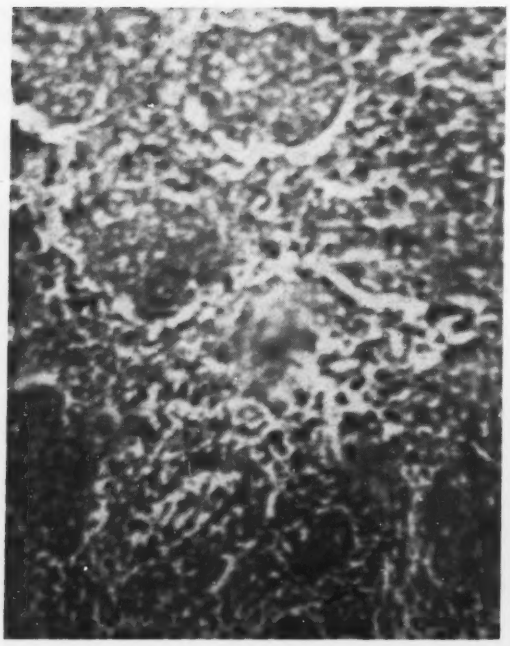

Figure 2

patient is unique in that he had bilateral growths. He is alive and well one year later.

CONCLUSION

An additional case, similar to those reported in the literature under the lymphoma group of parotid tumors, is recorded. The natural history of this lesion is fairly well known, although only a relatively small number have been reported. They are more common in women; tend to occur toward middle age; can recur locally; never metastasize, and can be bilateral. Lymphoepithelioma of the parotid responds to either surgery or radiation.

In the opinion of the authors this does not seem to be a malignant lesion.

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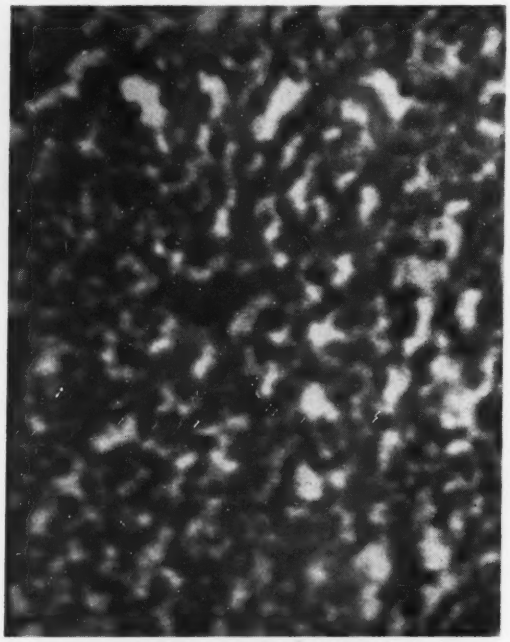

Figure 3

Some professional people know the price of everything and the value of nothing. Being exposed to the "gravy of grateful hearts" might change their views on public relations, which are the sum total of our private patient relationships and cannot be measured by surveys or bought with dollars.

Harlan English, M.D.
A.M.A. Delegate
Danville, Illinois

A Medical Student Looks at Blue Shield

Wilbur C. Pickett, Jr.

Baltimore, Maryland

The medical student of today finds his chosen profession in a dynamic state. Major social, economic, and political changes in recent years have had large effect in the medical field. The story of Blue Shield is in large measure the story of these changes and the adjustment of the medical profession to them.

The great depression centered national attention upon problems of individual security. Social security legislation illustrated the possibility of utilizing the sovereign powers of state or nation in the attempt to alleviate personal distress affecting large numbers of people. A climate of political experimentation made inevitable the advancement and advocacy of various proposals for the socialization of medicine.

The necessity for some concerted plan for dealing with the problems of medical costs had been suggested in the report of a five-year study by a committee headed by Dr. Ray Lyman Wilbur, a past president of the American Medical Association and then Secretary of the Interior in the cabinet of President Hoover. The majority report recommended that medical costs be financed through insurance or taxation or by such methods in combination.

A most significant development in the attitude of the medical profession toward the problem of medical costs occurred in September 1938 when the House of Delegates of the American Medical Association endorsed the principle of voluntary health insurance. This endorsement was the first of its nature. It occurred during a special session of the American Medical Association. It set the stage for a voluntary health program that has been called the greatest cooperative health effort in world history, and it occurred at a time when the power of the profession to control the economic pattern of medical practice was being seriously questioned.

The choice by the profession of voluntary medical prepayment plans as a means of adjustment to changing conditions was probably, as Cunningham suggests,[1] attributable to the phenomenal success of the community-wide non-profit Blue Cross plans for hospital care that originated at Baylor University in Dallas in 1929.

The first physician-sponsored prepayment plan to follow the 1938 American Medical Association endorsement of voluntary insurance was established by the California Medical Association on a non-profit basis in 1939. The Michigan State Medical Society followed the California group with a similar plan in 1940, shortly afterwards other state and county medical societies adopted similar prepayment plans, and what has subsequently become known as the Blue Shield Plan was under way. The plan represents an association of voluntary non-profit medically sponsored, medical care prepayment plans. The tremendous expansion of Blue Shield is reflected in the fact that in 1941 there were eight Blue Shield plans with a total of 370,000 members whereas by the end of 1953 there were 77 plans with 28,150,000 members.

The success of Blue Cross and Blue Shield programs is attributable in large part to the fact that in addition to acquiring large membership within themselves they catalyzed a voluntary health insurance movement that surpassed the success of any previous insurance program in history. Only in the wake of their success did commercial insurance companies awaken fully to the possibilities of the medical care market. Today Blue Shield plans write about 33 per cent of the surgical insurance and 47 per cent of the medical coverage; commercial plans account for 60 per cent of the surgical insurance and 39 per cent of the medical care insurance. Perhaps the best measure of the success that the voluntary plans have had in removing the economic barriers to medical care is reflected in the fact that approximately 100,000,000 Americans have enrolled in hospital or medical prepayment and insurance plans.[2]

Thus Blue Shield is the effective answer of organized medicine to a great and challenging socioeconomic problem—the problem of how best to meet the cost to the individual of serious medical emergencies. The problem is as old as civilization, but the ever-changing complexities of social organization give it a constantly new appearance and require that any plan for coping with it be flexible and subject to adjustment to the specific conditions of time and place. Blue Shield has the merit of that great quality.

The basic concept is that of insurance which involves what Sir Winston Churchill has called "the magic of averages applied to the salvation of the multitude." It is but natural and logical that any expansion of this principle should be applied to protect the individual against the loss of capital or credit or both as a result of illness. The conditions of its application, however, require much thought.

This essay won first prize in a national contest sponsored by Blue Shield and the Student American Medical Association. Mr. Pickett is a student at the University of Maryland.

The problem of how best to utilize the principle is essentially one for resolution by the medical profession because, despite the intrusion of social and economic considerations of a non-medical nature, the only comprehensive knowledge of the factors of controlling significance in any feasible plan is possessed by the medical profession. Quite obviously no other profession or group has had comparable experience with illness, its causes, costs, cures, and effects. The whole interplay of human relationships in respect to illness—actual, feigned, or anticipatory—is under the constant observation of the medical profession to a degree not even approximated by any other body of men.

It is for this reason, chiefly, that the medical profession—almost as a unit in this country—has rejected the concept of governmental responsibility for individual medical costs. The concurrence of other professions and groups, fortified by the adverse experience of those nations which have tried it, supports the view of the medical profession in this country that the occasional advantage to an individual of socialized medicine is much more than offset by its individual and group disadvantages.

All of the visualized values of socialized medicine —which have led to its adoption in some countries, such as England—can be realized through the wise employment of the related, but definitely distinct, concept of group responsibility through voluntary insurance without the sacrifice of those principles which have made America pre-eminent in the field of modern medicine.

The challenge to the medical profession implicit in the support of socialized medicine by influential persons and groups in this country is of especial interest to those of us who are medical students. The practitioners of tomorrow must come from our group and therefore we must expect to cope with the same basic problem and seek to carry forward the policies dictated by the experience and the judgment of our predecessors and elders.

Blue Shield has been built on principle and proved by experience. It is no criticism to say that some experimentation—with resultant failure as well as most encouraging success—has been necessary in the past or that future experimentation may be required in the effort to achieve maximum success. Some degree of experimentation with proper attention to the safeguards dictated by experience, principle, and judgment, is essential to progress in almost any field.

Medical men, because of their awareness of the problem of the potentially adverse effect of medical costs to the individual and their clear and full realization of the total non-desirability of socialized medicine as an attempted solution of the problem, are morally obligated to use all of the resources of the profession to see that acceptable methods of dealing with the entire problem are successful in the widest possible area and the highest possible degree.

One of the areas yet to be explored fully relates to the fixing of the point at which the advantages of early diagnosis as the result of examinations induced by insurance—which would not be made otherwise—may be offset by excessive or unwarranted demands for medical attention induced by the same factor. An insurance plan or contract cannot change human nature and there will always be individuals who are perverse as well as those who are merely unfortunate, but fortunately the principle of insurance rests on the laws of probability with respect to a group rather than the individuals comprising it. Thus it may be possible through safeguards yet to be devised to embrace the risks deriving from defects of character or judgment in the process of insuring against the costs of illness and minimizing its incidence. After all, bonding companies do survive. Certainly in any event it will be possible ultimately to determine with reasonable accuracy the point at which insurance ceases to be feasible.

The vast increase in recent years in the total volume of insurance for the prepayment of medical and hospital costs has been a most significant and desirable social development. Undoubtedly it has lessened the demand that would otherwise have existed for solution of the problem by political means. There can be no doubt either that the medical profession, through its sponsorship of various Blue Shield plans, has contributed enormously to the accomplishment of what has been done, both directly and indirectly. And it may be that the contribution made indirectly by forcing competitive plans of other sponsorship to provide wider coverage and more liberal protection will prove in the long run to have been the more important effect.

The overall success of Blue Shield is undoubtedly attributable to its insistence upon certain uniform conditions based on principles. Adhering to these principles and cautiously proceeding with the pioneering efforts to bring larger areas of medical costs within the protection of insurance, it is reasonable to anticipate a substantial solution of the entire problem.

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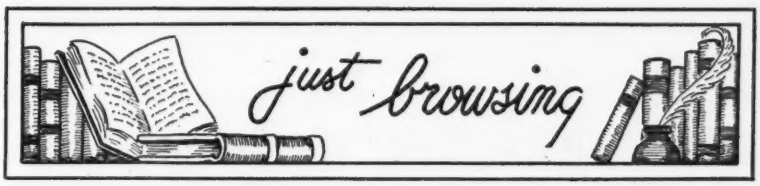
Health cannot be dissociated from the particular conditions under which man has to function. It implies fitness to his total environment.—*Rene J. Dubos, Ph.D., Nat. Tuberc. A. Tr., May, 1954.*



It was only about 70 years ago that the first writings about appendicitis appeared, and a hitherto unrecognized disease became one well known with well standardized treatment. Charles McBurney contributed so much to the diagnosis and treatment of the condition that mention of his name is apt to bring to the mind of the listener the disease appendicitis.

He is probably most famous for locating the point at which maximum tenderness is usually found—McBurney's point—and the gridiron type of incision so often used in operations for its removal—the McBurney incision.

Writing of his experiences with appendicitis, gained through his position as director of the surgical service at Roosevelt Hospital and professor of surgery in the College of Physicians and Surgeons, he said, ". . . I believe that in every case the seat of greatest pain, *determined by the pressure of one finger,* has been very exactly between an inch and a half and two inches from the anterior spinous process of the ilium on a straight line drawn from that process to the umbilicus. This may appear to be an affectation of accuracy, but, so far as my experience goes, the observation is correct." (This is not the point so often defined as McBurney's point—halfway between the anterior superior spine and the umbilicus.)

The McBurney incision as described in 1894 is not exactly as commonly used today, though basically it has remained unchanged.

". . . The incision in the skin is an oblique one about four inches long. It crosses a line drawn from the anterior iliac spine to the umbilicus nearly at right angles about one inch from the iliac spine, and is so situated that its upper third lies above that line. . . . The section of the external oblique muscle and aponeurosis should correspond, great care being taken to separate these tissues in the same line, *not cutting any fibers across.* This is easily accomplished.

". . . the fibers of the internal oblique and transversalis muscles can now be *separated,* without cutting more than an occasional fiber, in a line parallel with their course—that is, nearly at right angles to the incision in the external oblique aponeurosis.

"The transversalis fascia is thus well exposed and is then divided in the same line. Last of all the section of the peritoneum is made.

". . . The appendix having been taken away, the wound in the peritoneum, which is transverse, is then closed by suture. The similiar wound in the fascia transversalis is also sutured. The fibers of the internal oblique and transversalis muscles fall together as soon as the retractors are withdrawn, and with a couple of fine catgut stitches the closure can be made more complete. The wound in the external oblique aponeurosis is sewed with catgut from end to end. When the operation is completed it will be seen that the gridiron-like arrangement of the muscular and tendinous fibers, to which the abdominal wall largely owes its strength, is restored almost as completely as if no operation had been done. In performing this operation I have noticed several advantages.

"In the first place, muscular and tendinous fibers are separated, but not divided, so that muscular action cannot tend to draw the edges of the wound apart, but rather to actively approximate them. . . . The fascia transversalis not being drawn away by the retraction of the deepest layer of muscular fibers, this fascia is easily completely sutured, and thus greater strength of repair is assured. No muscular fibers or larger nerves having been divided, pain after operation is almost absent. . . ." (This comment about its advantages has such a familiar ring that it could almost pass for a present-day comment of an advocate of transverse abdominal incisions. Such advantages, it seems, were recognized a long time ago.)

McBurney described some disadvantages of this newly-described incision, sounding the final warning that "it is not an easy operation, and should not be attempted by those who are unfamiliar with operations upon the appendix" —a discouraging comment for present day interns and residents!—*O.R.C.*

PRESIDENT'S PAGE

The President's Page this month consists of a letter to Doctors Karl A. and W. C. Menninger.

DEAR KARL AND BILL:

This letter is publicly addressed to you as the sons of Dr. C. F. Menninger. In thinking over how I could best promote the activities of the Kansas Medical Society Committee on History and the plans for our centennial celebration three years from now, it occurred to me that Kansas physicians who have practiced with their fathers would have a unique slant on medical history of the state.

There are, of course, many possibilities to write in this regard: Murray Eddy, Don Medearis, Harold Neptune, Howard and Cecil Snyder, Jim Colt, and dozens of others. I chose you two because it is now almost 50 years since I used to sit in the Presbyterian Church in Topeka and in dull moments of S. S. Estey's sermons study the backs of your necks and the slant of your ears. In those days your chemist brother and your incomparable mother sat with you. Dr. C. F. passed the collection plate, I believe, but as I was not a paying guest that memory is uncertain.

In spite of this Sunday association, the Porters were patients of Dr. McGuire and with all due regard to your father, they didn't come any better in those days than Dr. McGuire. One of the highest honors that ever came to me in my home town was when I returned to Topeka with my medical degree, called on Dr. McGuire, and as we left his office heard him tell his "boy" to "shine Dr. Porter's shoes, too."

These memories of C. F. Menninger passing a collection plate, C. A. McGuire with his colored boy and the like multiplied to the nth degree make up the history of Kansas medicine. You who were fortunate enough to be associated intimately with these men owe the rest of us the obligation of getting your memories down on paper before you, too, are history.

Dr. Merrill Mills, chairman of the Committee on History, is waiting to hear from you.

Sincerely yours,

J. M. Porter

As this issue of the JOURNAL goes to press word has just been received of the tragic and untimely death of Dr. Porter. The entire membership of the Society joins in extending sympathy to Mrs. Porter and the family.

—Editor.

EDITORIAL COMMENT

Tuberculosis Survey

The Kansas Tuberculosis and Health Association is conducting a state-wide survey on tuberculosis beginning early this fall. They hope the medical profession will cooperate in making this a useful undertaking.

This plan was announced at a meeting in Topeka on June 23 which was attended by some dozen physicians including John M. Porter, president of the Kansas Medical Society, and Joseph W. Spearing, chairman of the Committee on Control of Tuberculosis.

Dr. Ralph I. Canuteson, president of the Kansas Tuberculosis and Health Association, introduced Dr. Joseph B. Stocklen, controller of tuberculosis in Cuyahoga County, Cleveland, who has been selected to direct the survey. He explained what the survey hoped to accomplish and how it would be carried on.

Dr. Stocklen began by agreeing that an out-of-state team can approach such a survey with less bias than if it were locally conducted. This is strictly a survey, a study of a problem with recommendations for possible improvements. The study will attempt to learn the existing conditions in relation to tuberculosis control in Kansas.

It is already known that Kansas has a record that is currently much better than the national picture, that this death rate is 5 and the national figure is 11 per 100,000. It is also known that there are spots in this state that need improvement and, of more serious consequence, that the incidence of tuberculosis in Kansas appears to be rising.

Dr. Stocklen briefly reviewed the dramatic decline in the disease during the last hundred years. As a result of this success, apparently the public and the medical profession lost interest, which might have important repercussions. He recalled tuberculosis to be a cyclic disease and wondered if once again there will be a race of people susceptible to tuberculosis at a time when the germs are resistant to the drugs that are now used in its treatment.

This nation, and notably Kansas, is now at the crossroads where some decision must be made. The survey is designed to give the people of this state the facts so they can more intelligently elect the course they shall take in the future. The decision as well as knowledge of the present situation rests largely with the medical profession, so the doctor is the key to the survey and his cooperation is essential for its success.

Dr. Stocklen suggested they would like to know answers to questions like the following:

1. Where are the known active cases which are not hospitalized?
2. How many are under treatment?
3. Why are unhospitalized cases not hospitalized?
4. How many private physicians have patients under their care?
5. How can the tuberculosis control program best meet the needs?
6. What about hospitalization and follow-up measures?
7. What about the use of BCG?
8. Is tuberculin testing in order now that we have such a low morbidity and mortality rate?
9. What is being done in the rehabilitation of the tuberculosis patient?
10. How many recalcitrant patients are there?
11. Is more money needed at the sanatorium?

The Committee on Control of Tuberculosis met on August 7 and voted to cooperate with this survey. Sometime in the fall each member will receive a brief questionnaire. Your committee respectfully urges that each physician give the very few moments it will take to reply. This will be a major project of your committee during the coming year and its success, its value to the public, will be determined by the degree to which the practicing physician assists in providing the necessary information.

Health Agencies

In the July *Northwest Medicine* an author stated that out of some 2,800 nationwide charities at least 80 are devoted to health. Each is dedicated to the relief of patients suffering from some condition or to eradicating the condition, or at least to educating the public about the condition. So each is serving a worthwhile purpose, each will gladly accept contributions, and each would possibly welcome an endorsement from organized medicine.

That, of course, means only the 80 health agencies. The other 2,720 will accept contributions but probably have less use for medical endorsements since their charities are not related directly to health. And yet who would say that CARE and many others in that classification have no bearing on health. So of course the boundaries are not well marked unless the name identifies their purpose. And there you have 80.

There are, for example, at least 12 on the subject of blindness, six on cancer, and a couple on leprosy. There is more than one charity that overlaps with others in names, even if this is not necessarily true of their services, as in the case of the National Council to Combat Blindness and the National Society for Prevention of Blindness.

Many have made themselves known in one way

or another. Perhaps the most surprising feature of the list is that there are so few strange names, which indicates at least that people are aware of their presence whether or not anything is known of their purpose. New to this writer are the Common Cold Foundation and the Foundation for the Study and Aid of the Emotionally Unstable Personality.

Perhaps these are newcomers, but we are glad they are among us even if their presence has previously been unknown. Medicine working without a lay agency has been handicapped in each of these fields, as can readily be seen by our lack of progress in conquering these most distressing conditions.

With some of the other health agencies now so apparently successful in their various tasks that they have nothing further to do, perhaps the public can really get behind a drive to conquer the common cold and to stabilize the unstable personality.

So give a dollar to spare humanity this untold suffering. Certainly the common cold contribution can be sent in care of your postmaster like so many similar donations. But the other, we don't know. Just mark your envelope UNSTABLE PERSONALITY, and perhaps we shouldn't tell you where to send it. Perhaps we shouldn't even think what we are thinking.

Social Security Revisions

A bill to revise the Social Security law passed the House recently and will come up for consideration by the Senate in the next session. As on any controversial subject, many opinions have been expressed and many more will be heard before the Senate takes action. The matter is called to the attention of Kansas physicians now to give them an opportunity to discuss it with their senators who will be at home until Congress convenes in January.

An interpretation of the proposed revisions was carried in the *Chicago Daily News* on July 20 under the heading "Someone Must Pay," and was sent to the Kansas Medical Society by the American Medical Association. The editorial follows:

In a whooping anticipation of elections ahead, the House passed sweeping revisions in the Social Security law by a vote of 372-31. The bill now goes to the Senate where, we earnestly hope, an effort will be made to find out what the taxpayers are getting into.

As with all "welfare" legislation, it is not a pleasant task to quarrel with kindly, humane proposals. It is certainly true, as the House noted, that wives are quite often a few years younger than husbands. Hence it seems reasonable to lower from 65 to 62 the age at which women qualify for old-age annuities.

That way, a couple could have a more substantial income, perhaps enabling the husband to retire at 65 when he might otherwise be unable to do so. For widows and woman workers—although they live longer than men on the average—the lowered age can be justified on the basis of gallantry, equal treatment, or something.

The House legislation comes on the heels of administration-sponsored improvements last year, extending benefits and bringing coverage to some 10 million additional persons.

Barron's Weekly points out that in 1950, the Social Security system was paying an average of $21 monthly to some 2.9 million persons. By June, 1954, payments were being made to 6.5 million individuals, at an average monthly rate of more than $50.

Thus what started out as a modest program for a minimum pension of bare-sustenance proportions is mushrooming into a system promising a comfortable living for the retired, care for the disabled and dependent, and with increasing inequalities between contributions and benefits.

As we said, the advocate of caution in this progress has an ungrateful role, something like parading around the feast with a stomach pump. For who can gracefully oppose benefits for women at 62? Or 60? Or even 50? Who can argue that payments to disabled children or their widowed mothers should stop at age 18?

The fact remains, however, that these things cost money. The Social Security system is still young. It has a surplus of $22 billion in its accounts—although the money is spent and what it has are government bonds. But the fund is piling up obligations faster than it is reserves, and sharply higher taxes for the system are already in the works.

One has only to look at the rates which private insurance companies charge for similar insurance, or deferred annuities, to realize what a tremendous "bargain" the Social Security system seems to be offering. To what extent this something-for-nothing offer is a fraud upon future taxpayers is a question that sorely needs an answer.

The House did not even hold hearings upon its bill to add $2 billion a year to Social Security costs. The Senate indicates that it will not be similarly stampeded. It should not be.

The hard truth is that the government cannot pay money to one person without having previously taken it from him or some other person. The great popular appeal of Social Security, of course, rests upon the belief that somebody else is going to get the heavy end of the check.

This expectation could be illusory for so many millions of taxpayers that a sober estimate of how many billions the government is promising, and how it will

be paid for, is imperative before we go farther.

It would be unthinkable for some future Congress to reneg on a contract sealed by the payment of taxes. But we also have no moral right to obligate future taxpayers to a burden that could become so great as to lower their own standard of living, while they pay for the generous but ill-advised impulses of their predecessors.

Booklets for Patient Education

Answers to many questions in the minds of the public can be provided in the reception room of the doctor's office. There are many avenues of education, but still the most reliable information is that which comes from the medical profession itself. Lacking time to discuss the multiple subjects in which patients are interested, the doctor may still disseminate good ideas through the reading material he keeps in his reception room.

The American Medical Association publishes many pamphlets which are distributed to physicians without charge upon request. Those who have never read these leaflets will be surprised at the amount of information that is presented in an interesting manner for the layman.

The latest publication is a 12-page booklet entitled *To All My Patients.* In addition to discussing medical and hospital fees and health insurance, it tells the roles of various persons on the medical team in providing good medical care.

There are many others. Subjects such as *Quacks, On Guard, Health Today,* and *A Doctor for You* are but a few. The one called *Quacks* points out the danger of unscientific healing and tells of various methods used by different cultists. *On Guard* relates a brief description of the A.M.A.'s drug evaluation program. *Health Today* discusses medical progress over the past 50 years. *A Doctor for You* suggests ways for small communities to attract doctors.

These and many other pamphlets are available to physicians. They may be secured from the Kansas Medical Society or from the Department of Public Relations, American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

The Middlesex County (Connecticut) Medical Association has issued a 16-page guide to community health services and is distributing it to residents with the help of the woman's auxiliary. The booklet describes the training and responsibilities of the family physician, encourages selection of a regular physician, outlines the association's 24-hour emergency phone system, and includes a roster of its members.

Kansans on National Committees

Two Kansans, Dr. Clarence H. Benage of Pittsburg and Dr. George F. Gsell of Wichita, are now serving on national committees appointed by the American Medical Association to study important subjects. Dr. Benage is a member of the Committee on Nursing Service, and Dr. Gsell is one of a group which will review the functions of the Joint Commission on Accreditation of Hospitals.

Dr. Benage will work with seven others on the full committee. He is also a member of a sub-committee appointed to survey schools of nursing.

The committee on which Dr. Gsell is serving was formed after the House of Delegates, at its June meeting in Atlantic City, adopted the following recommendation: "Your Reference Committee recommends that the Speaker of the House of Delegates be requested to appoint a special committee to review the functions of the Joint Commission on Accreditation of Hospitals to consist of seven members, none of whom shall be members of the Council on Medical Education and Hospitals or of the Joint Commission on Accreditation of Hospitals. The special committee should be instructed to make an independent study or survey and report its findings and recommendations to the House at the next annual meeting. All physicians and hospitals are urged to pass on to this special committee any observations or suggestions concerning the functioning of the Joint Commission on Accreditation of Hospitals."

Both Kansas physicians will welcome opinions and suggestions from members of the Kansas Medical Society.

Kansas City Clinical Conference

The annual conference of the Kansas City Southwest Clinical Society will be held at the Municipal Auditorium, Kansas City, Missouri, October 3-6. Fifteen guest participants will give lectures and conduct panel discussions and conferences. Television programs in color will depict operative clinics and clinical demonstrations. The Edward Holman Skinner memorial lecture will be given by Dr. Eugene P. Pendergrass, professor of radiology at the University of Pennsylvania.

Information and programs may be secured from the Society, 3036 Gillham Road, Kansas City 8, Missouri.

Annual grants to states for maternal and child health services, which started at $3,624,000, now total $11,927,700 for the fiscal year 1956.

Multiple Polyposis and Carcinomatosis

Tumor Conference

Edited by Bernard Klionsky, M.D.

Multiple polyposis with carcinomatosis is a most unusual condition and presents several interesting problems of differential diagnosis and of therapy.

Dr. Burger: The patient is a 28-year-old white man who was first admitted to the University of Kansas Medical Center three years ago. Three days before admission he had noted fever, malaise, and diarrhea. He was seen by his family doctor who treated him with paregoric; his condition did not improve. Following an increase in tenderness in the lower portion of his abdomen, he was admitted to the hospital.

He was examined by members of the hospital staff who agreed that he was acutely ill and that a laparotomy was indicated. An operation was performed at which the surgeon found a sealed-off perforation of the sigmoid colon. After a somewhat stormy postoperative course, he improved. He was examined with a sigmoidoscope, and many polyps were found within the rectum. He then had a barium enema which revealed multiple polyposis of the colon; there was something in the study which was suggestive of a carcinoma of the sigmoid. Following this he had a subtotal colectomy. The ileum was anastomosed to the distal portion of the sigmoid.

He returned one year later with a recurrence of tumor in the anterior abdominal wall. This was removed, and no further evidence of metastatic tumor was found. One year following this a rectal polyp was seen with a proctoscope and was removed surgically. The pathological diagnosis at that time was atypism with no evidence of tumor.

He returned again recently, having noticed a mass in the anterior abdominal wall beneath the old incision. This was thought to be a recurrence of the tumor. At laparotomy there were no metastases to the liver. However, the cul-de-sac, adjacent to the bladder, was crowded with tumor. Biopsy was done and was reported as metastatic carcinoma.

Dr. Goertz: These roentgenograms were taken on his original admission. There is marked narrowing in the sigmoid which is seen fairly clearly at the distal end. This is an air-contrast study which shows multiple polyps throughout the colon, and there is an area where there is a sharp cut-off (Figure 1). An evacuation film doesn't show the polyps quite as accurately as the air study does.

These roentgenograms were taken in 1953 when he first came back with the metastatic nodule in his abdominal wall incision. Markers were taped directly over the nodule to see whether there was any direct relationship between it and the bowel.

Dr. Helwig: Was colectomy done on this individual?

Dr. Burger: It was. A subtotal colectomy was performed shortly after closure of the perforation of the sigmoid.

Dr. Helwig: The original growth was a rather classic low grade papillary type of adenocarcinoma. It produced a fair amount of mucus, as so often these colonic tumors do, and extended beneath the mucosa and almost through the bowel wall.

The biopsy of the non-infiltrating polyp shows a sharp transition from normal mucosa into this abnormal polyp. There is little loss of polarity of cells, but there are scattered foci of cellular atypia on the end of the polyp, as seen in many polyps. At this stage they are not true invasive malignant neoplasms.

We have here a rather classical story of multiple

Figure 1. Air contrast roentgenogram revealing multiple polyps throughout the colon and an area of constriction in the sigmoid colon.

Cancer teaching activities at the University of Kansas Medical Center are aided by grants from the National Cancer Institute, U. S. Public Health Service and the Kansas Division of the American Cancer Society. Dr. Klionsky is a Clinical Fellow of the American Cancer Society.

polyposis and of malignancy at an early age. It is typical of patients with polyposis that cancer does occur at an early age, as a rule many years earlier than most other multiple cancers. The youngest such patient I have observed was a boy of 14 who had four cancers in the colon with massive metastasis in the liver. There was no family history of polyposis; this is not uncommon.

Dr. Stowell: Dr. Friesen, will you discuss this case for us?

Dr. Friesen: This is a case of a young man with polyposis with malignant change. He was first seen at the age of 25. I think it is significant that his first symptoms were those of perforation. This is not the first patient I have seen who, in his 20's, presented with acute abdominal pain with perforation as the first symptom of carcinoma of the colon. This man, even though he has carcinomatosis, even now is a big strapping healthy-looking fellow who had not lost weight appreciably until just recently. It is very easy to become completely pessimistic about this situation of polyposis with malignant change. There are, however, a few patients who have apparently had their disease arrested. This patient had good surgical treatment early. A subtotal colectomy was done for polyposis and for the carcinoma. However, this man developed metastases and other polyps in the remaining rectum.

Dr. Stowell: Do you have any suggestions as to what one should do in cases of this kind, Dr. Friesen? When should one become radical, and how radical?

Dr. Friesen: Patients with true polyposis should have the colon removed. However, there is lots of discussion among surgeons in this counrty about whether one should leave the rectum in. This patient's rectum was left. Some surgeons would not only have done a total colectomy but would also have removed his rectum, leaving the patient with an ileostomy. An ileostomy is a very difficult thing with which to cope. I myself wouldn't want to live with such a drainage for a number of years, so I have felt that it is best to leave the rectum in and to fulgurate the polyps that remain in the rectum or as they develop. However, that management was carried out on this patient, and here he is now with carcinoma in the rectum and helpless. Perhaps if he had had a rectal excision at the time he had the colon excision he might not have carcinomatosis today. I think that is too difficult a question to answer, and chances are that he might then have had carcinoma in his lymph nodes as he does at the present time.

Dr. Stowell: When one finds a substantial number of polyps in an individual, what should be the therapy? Some might suggest watching the polyps and having the patient come back for repeated observations.

Dr. Friesen: That is too dangerous. The incidence of cancer in multiple polyposis is so high that such patients must be treated immediately with at least a subtotal colectomy, or perhaps a total colectomy with removal of the rectum.

Dr. Helwig: You mean the minute the diagnosis is made, whether they have cancer or not? I think that is a very wise thing.

Dr. Friesen: Yes. Even though there is no cancer demonstrated I think this is certainly indicated.

Dr. Helwig: We studied a family in which a woman had familial polyposis. Her sister was examined by barium enema and proctoscopy and was found to have polyposis without any symptoms at all; but we did a total colectomy on her also because almost 100 per cent of such persons who live long enough get cancer.

Student: Was the rectum removed on this lady?

Dr. Helwig: No. She comes in at intervals, and if she has any polyps they are removed.

Student: How much would you raise the mortality rate by doing a total colectomy with removal of the rectum?

Dr. Friesen: I don't think the mortality rate would rise appreciably, but the morbidity rate would be markedly increased. In addition to increased technical difficulties imposed by a more extensive surgical procedure, there are problems relating to the ileostomy which is required. Many patients have dysfunction of the ileostomy, have difficulty in taking care of it, and suffer erosion of the skin. It presents a real problem. Many of the patients who have an ileostomy are doomed to a singularly lonely life. On the other hand there have been many recent improvements in the techniques of making and managing ileostomies. Many people get along quite satisfactorily.

Dr. Joffe: In the absence of a family history, how many polyps must you find before making the diagnosis of multiple polyposis?

Dr. Stowell: I was hoping someone would ask that question. I would like to hear some serious discussion of this question, because the presence of two or more polyps is not unusual in individuals with no history of familial polyposis.

Dr. Friesen: I think there must be two disease entities. There is the young person with hundreds of polyps; the older person, whom we see quite often with one, two, three, or four polyps, rarely has more than that. I think each polyp is as dangerous as the other.

Dr. Joffe: Do you offer colectomy to older individuals with a few polyps?

Dr. Friesen: No. If there is one polyp, it should

be removed locally via the sigmoidoscope or at laparotomy. One should of course make sure that the patient doesn't have a cancer and that the polyp is not malignant. If the polyp is malignant, that patient should be treated as if he had a malignancy. An appropriate partial colectomy should be done, at which time it should be determined whether there are more polyps. If there are more polyps, then I think that each of them should be removed and examined microscopically. If any one of them is malignant, an appropriate cancer operation should be done.

Dr. Stowell: This is perhaps of more interest to pathologists than to others. About a year ago Leuchtenberger[1] claimed to find inclusion bodies in polyps in the colon that are undergoing malignant change. It would be interesting to study the histologic material in a case of familial polyposis with that concept in view.

Dr. Friesen: Does this imply a viral origin?

Dr. Stowell: The author did not state that in her paper, but she mentioned the possibility in personal discussions.

Dr. Delp, would you care to comment on the disease condition of this case?

Dr. Delp: Patients with polyposis often have diarrhea which may be diagnosed as colitis for some time before its true cause is discovered. Investigation with barium enema or a sigmoidoscopic examination reveals the polyps. A continuous diarrhea makes one suspicious, but it can be relatively mild. It's of further interest because occasionally you find a patient with true ulcerative colitis who has a pseudo-polyposis, which can be demonstrated by x-ray. I suppose, by some surgical standards, there are suregons who would say that this is an indication for colectomy too. On the other hand, I think that this group of patients often gets by without surgery. If they have a remission, and this I have seen demonstrated in several cases, these pseudo-polyps will disappear completely.

Dr. Stowell: It is also interesting that some of these ulcerative conditions of the colon are associated with an increased incidence of carcinoma.

Dr. Pollak: Dr. Helwig, I have the impression that carcinoma of the colon, while extremely rare in the age groups of the 20's and early 30's, runs a particularly rapid course when it does occur in persons of that age group.

Dr. Helwig: That has been true in the cases I have followed. Of course one doesn't see many cases of this in a lifetime. I heard Dr. Wangensteen make a statement that he was strongly of the opinion that one should probably do total colectomies, perhaps in all cases of carcinoma of the colon, because of the rather significant incidence of polyps elsewhere in the colon. I think that the incidence was about 10 per cent.

Dr. Friesen: That seems like rather extensive surgery for the additional polyps which may be present in the 10 per cent of patients with cancer of the colon. There is another way to discover the polyps. One can do a hemi-colectomy for the primary malignancy and ask the pathologist to open and examine the whole specimen before anastomosing or finishing the operation. If there is another polyp in this half of the colon, then one can look into the other half with a sigmoidoscope and examine carefully the entire mucosal surface. If there are no polyps, the other half need not be removed. Only about 10 per cent of patients with carcinoma of the colon have additional polyps. I think that this is not a high enough incidence to warrant a complete colectomy.

Dr. Helwig: I would like to ask Dr. Delp a question. The literature in the last three or four years has contained many discussions of the incidence of carcinoma as a complication of ulcerative colitis. Cancer of the colon has been said to be up to a hundred or a thousand times more frequent in patients with ulcerative colitis than in the general population. We believe that for some strange reason carcinoma in ulcerative colitis usually runs a rapidly fatal course. In your experience, what relationship is there between ulcerative colitis and carcinoma?

Dr. Delp: I have certainly noticed the definite more frequent development of carcinoma of the colon in patients with ulcerative colitis. I am not yet so concerned about that increase in incidence to suggest that total colectomy is the treatment of choice in ulcerative colitis.

Dr. Stowell: This certainly is an interesting case of a rare condition which, among other things, illustrates a possibility at least of prevention of cancer. It remains a moot point as to how much one can accomplish by prophylactic removal of polyps.

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Copies of Hippocratic Oath Available

The A.M.A. announces that two-color offset reproductions of the Hippocratic Oath are available from its Order Department at $1.00 each. Printed on parchment stock, the reproduction measures 11¾ by 15¼ inches and is suitable for framing. Many physicians are placing copies of the oath in their offices and waiting rooms.

ACTIVITIES OF MEMBERS

Dr. D. Cramer Reed, who recently completed a residency in urology at the Medical College of Virginia, has returned to Wichita and is now associated in practice with Dr. H. F. O'Donnell and Dr. William H. Browning.

Three Kansas physicians, Dr. Walter Furst of Norton, Dr. Benjamin Matassarin of Wichita, and Dr. L. E. Peckenschneider of Halstead, recently received fellowship certificates from the American College of Chest Physicians.

Dr. Ralph H. Major, professor emeritus of the history of medicine at the University of Kansas Medical Center, contributed the article on "Diagnosis" to the 1955 edition of the *Encyclopedia Britannica.*

Dr. Franklin D. Murphy, chancellor of the University of Kansas, received an honorary Doctor of Science degree from the University of Pennsylvania in June at the university's 199th annual commencement exercises.

Dr. S. A. Scimeca, who formerly practiced in Caney and has recently been practicing in St. John, has returned to Caney to re-establish his practice there.

Dr. James G. Stewart, Topeka, was recently elected president of the Shawnee Guidance Center board of directors.

The Gelvin-Haughey Clinic, Concordia, announces that Dr. Foxhall P. Thornton, Jr., is now a member of its staff. Dr. Thornton is a graduate of the University of Virginia Department of Medicine and, after his internship at Boston City Hospital, served a residency in internal medicine at the University of Virginia Hospital and a residency in gastroenterology at the VA Hospital in Richmond, Virginia.

Dr. Gerhart R. Tonn, who has been serving a tour of duty with the military forces, has returned to his civilian practice in Wichita.

Dr. C. Frederick Kittle, assistant professor of surgery at the University of Kansas Medical Center, was recently elected to membership in the North American Chapter of the International Society of Angiology.

Dr. Girard Veenschoten, who has been practicing at Jetmore since 1952, recently moved to Hesperia, Michigan, to practice there.

DEATH NOTICES

Seth A. Hammel, M.D.

Dr. Seth A. Hammel, 76, an active member of the Shawnee County Society, died at a Topeka hospital on July 28. A native Topekan, Dr. Hammel opened an office in the city in 1905, after graduation from the University of Illinois College of Medicine and internship at Chicago Polyclinic Hospital. He also was an instructor at the Kansas Medical School, Topeka.

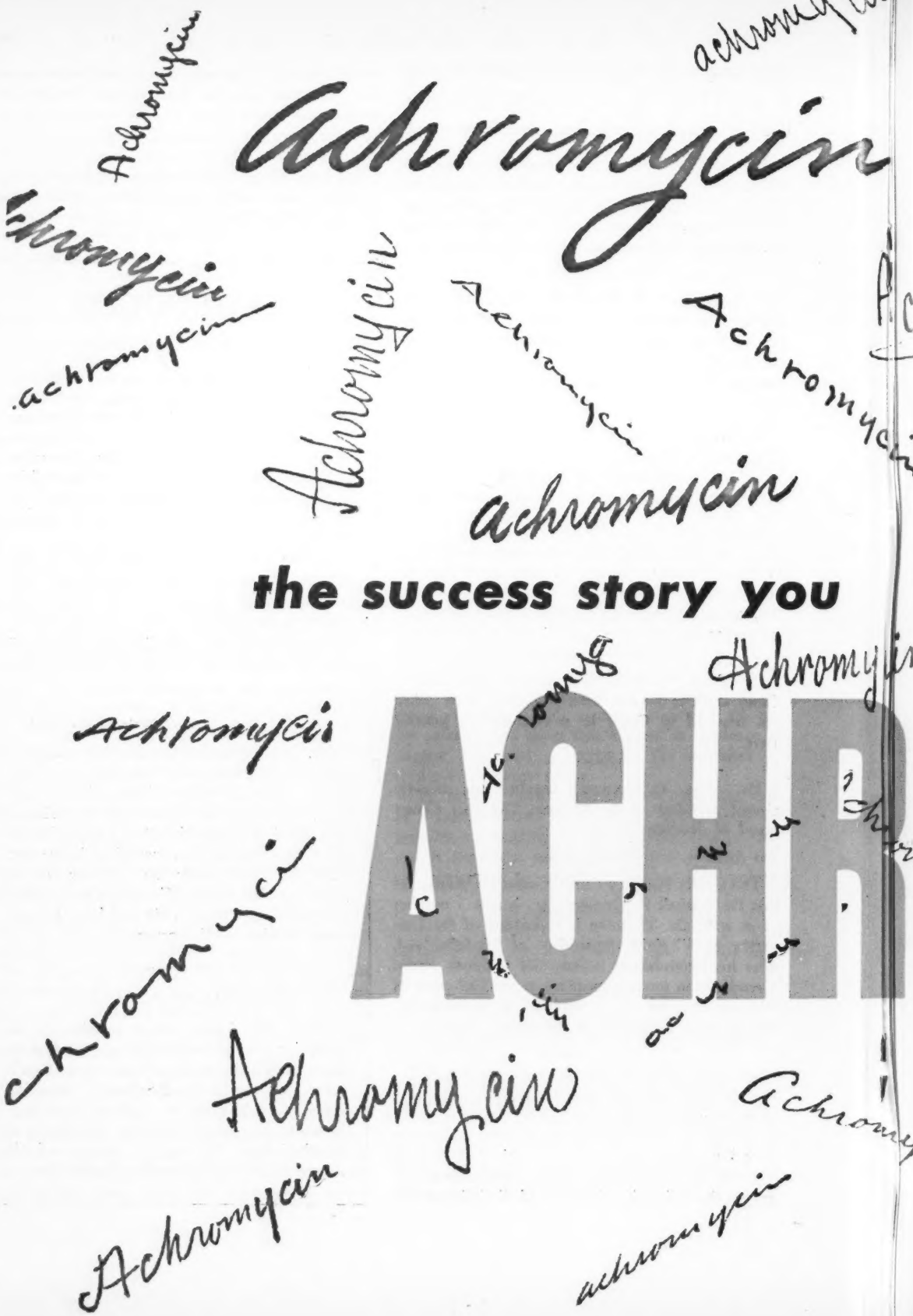
At the beginning of World War I, Dr. Hammel organized a field hospital unit and commanded that company. On his return from service he became state surgeon for the Kansas National Guard, and during World War II he was medical officer for Kansas Selective Service.

Charles Willard Longenecker, M.D.

Dr. C. W. Longenecker, 83, who had practiced in Kingman more than 40 years, died there on August 6 after an illness of four years. Dr. Longenecker was graduated from Kansas City Medical College in 1899. During his active years in practice, he specialized in eye, ear, nose, and throat work. He formerly was an active member of the Kingman County Medical Society and since 1941 had been an honorary member of the group.

James Harlan Adams, M.D.

Dr. J. H. Adams, 80, a member of the Sedgwick County Medical Society, died at his home in Wichita on August 17. He was graduated from the Southwest School of Medicine, Kansas City, Missouri, in 1914 and immediately began practice in Wichita, specializing in anesthesiology. He was a member of the American Society of Anesthesiologists, Inc.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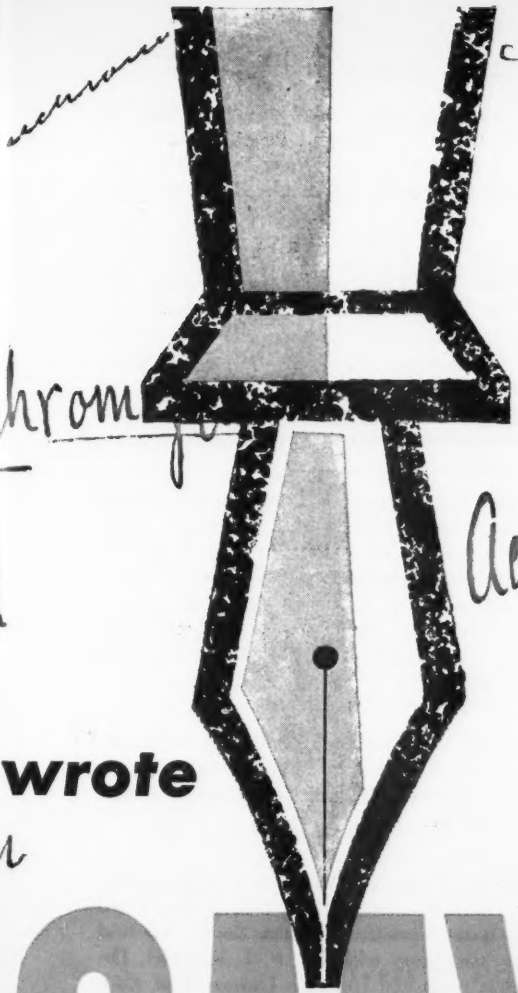

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Dr. Noble P. Sherwood, professor emeritus of bacteriology at the University of Kansas, Lawrence, has accepted a position as visiting professor of microbiology at the University of Indonesia School of Medicine, Djakarta, Java. He will leave in October and will have a short period of indoctrination at the University of California, Berkeley.

Dr. R. L. Drake, Dr. Bert E. Stofer, and Dr. L. E. Vin Zant, Wichita, are authors of a paper, "Ectopic Pinealoma," published in the July issue of *Neurology*.

At an organizational meeting of the Sedgwick County Chapter of the American Diabetic Association held June 29, the following Wichita physicians were elected to office: president, Dr. John L. Kleinheksel; vice-president, Dr. Benjamin M. Matassarin; secretary, Dr. Gary B. Wood, and treasurer, Dr. Ruth Page.

Dr. Clayton T. Ralls, Winfield, who has been engaged in practice there for 50 years, was guest of honor at a dinner given by the Winfield Academy of Medicine on July 28. At that time the Cowley County Medical Society presented him with an engraved 50-year key.

Dr. Melvin V. Holman, Wichita, has enrolled for a year's postgraduate work in anesthesiology at the University of Kansas School of Medicine.

Dr. Thomas G. Orr, Sr., professor emeritus of surgery at the University of Kansas School of Medicine, received an honorary Doctor of Science degree from the University of Missouri at its annual graduation ceremonies.

Dr. Ernest E. Harvey, Salina, has resigned as health officer for Saline County. A plan for a city-county health department has been adopted there, and Dr. Howard Wagenblast, who recently received a master's degree in public health from the University of California, has been employed as director. Dr. Wagenblast formerly held public health positions in Wichita and Lawrence.

The Axtell Clinic, Newton, announces that Dr. Charles Isaac is now a member of its staff and will specialize in urology. Dr. Isaac, son of Dr. Arnold G. Isaac, recently completed a three-year residency at the University of Kansas Medical Center. His wife, Dr. Anita Isaac, will announce plans later to practice in Newton.

Dr. William A. Nixon, who will leave soon to begin study at the University of Pennsylvania Graduate School of Medicine, was honored by 500 residents of Macksville at a community dinner on July 29.

Dr. Robert W. Blackburn, Council Grove, announces that Dr. James H. Davis is now associated with him in practice. Dr. Davis, a graduate of the University of Kansas School of Medicine, recently completed internship at George Washington University Hospitals, Washington, D. C. He will spend three afternoons each week at an office in Alta Vista.

Dr. Edward D. Greenwood, of the Menninger Foundation, Topeka, was an official member of the United States delegation to the first United Nations Conference on the Prevention of Crime and Treatment of Offenders, held in Geneva in late August and early September. He then went to Denmark to participate in a session of the International Union for Child Welfare.

Dr. George E. Burket, Kingman, went to Boston last month to enroll for a postgraduate course in surgery at Harvard Medical Center. He will complete the work next June.

Dr. Bartlett W. Ramsey, who was recently released from the service after two years at Walter Reed Hospital, is now practicing at the Topeka Medical Center in association with Dr. B. I. Krehbiel. Dr. Ramsey was graduated from the University of Kansas School of Medicine and served his internship and residency in pediatrics at the University of Kansas Medical Center.

Dr. Leo K. Crumpacker, Wichita, addressed the Rotary Club in El Dorado in August on the subject of cancer research and treatment. Dr. Ralph J. Metcalf, El Dorado, was Rotarian of the Day.

Progress in Treatment of Children

Twenty years of progress in the treatment of children by public and private agencies concerned with child health and welfare are reviewed in the July-August issue of *Children,* a publication of the Children's Bureau. The issue was prepared as part of the observance of the 20th anniversary of the passage of the Social Security Act on August 14, 1935. Copies may be secured for 25 cents from the Superintendent of Documents, Government Printing Office, Washington 25, D. C.

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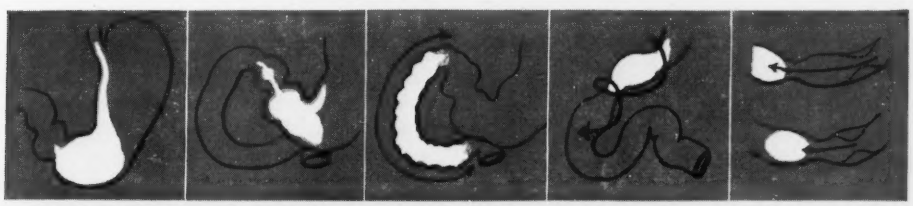

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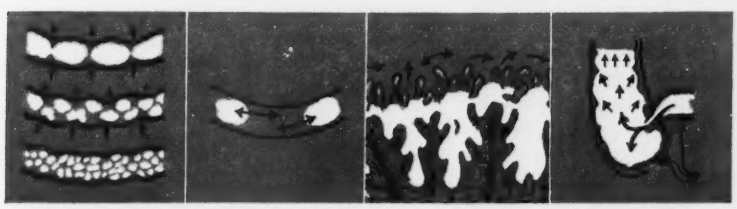

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SEARLE

THE MONTH IN WASHINGTON

Editor's Note. The following summary of Washington news was prepared by the Washington office of the A.M.A. for distribution to state and regional medical journals.

Although very little health legislation actually was enacted in the first session of the 84th Congress, a number of important bills made enough progress to insure they will get serious consideration when the second session starts next January.

Foremost is a bill to amend the social security act, and, among other things provide OASI payments for disabled workers after age 50. The present provision (enacted in 1954) protects a disabled worker's pension so it is not decreased because of his years of unemployment, but payments don't begin until he reaches 65.

The new plan, sponsored by Democratic members of the House Ways and Means Committee, was rolled through the House after closed committee hearings. But when it got to the Senate, Chairman Harry Byrd of the Finance Committee held it up, saying it was too important to be reported out without the complete hearings he plans for next session.

The American Medical Association is flatly opposed to cash disability insurance. One important reason is the association's conviction that federal machinery necessary to regulate disability examinations inevitably would project the government into the medical care field. There are many other reasons, including the relationship between cash payments for disability and the patient's interest in rehabilitation. The issue of disability pensions will be settled next year in the Byrd committee or on the Senate floor.

A bill for $90 million in grants for building and equipping non-federal research facilities passed the Senate and is awaiting action in the House Interstate and Foreign Commerce Committee. Hearings have been held on a bill for U. S. grants to medical schools and on another (Jenkins-Keogh) to allow self-employed persons to defer income tax payments on part of their income put into annuities.

Other bills that will be ready for action in January include legislation to stimulate nursing education, improve the medical care of military dependents, authorize health insurance for government workers, authorize U. S. guarantee of mortgages on health facilities, and offer military medical scholarships. The administration's bill for reinsuring health insurance plans by now is a little shopworn, but it still might be pushed again next year.

President Eisenhower has made it known he wants Congress to get to work on health legislation early next session. His urging might not be needed. Next year is a presidential election year, and both parties will exert themselves to enact, and take credit for, new health programs that carry public appeal.

Despite the hundreds of hours of hearings in Senate and House, not a single important permanent medical program was set up by Congress in the last session. A national mental health survey, supported by the A.M.A., was enacted, but the administration's plan for mental health grants will be up for action next year.

Ignoring protests of physicians and dentists, Congress extended the doctor draft act for another two years, after first adopting two amendments. It exempted all men over 45, and all 35 or older who previously had been rejected for medical commissions for physical reasons alone.

For almost four months Congressional committees pondered what to do about Salk poliomyelitis vaccine. At first there were two main questions: (1) How much money should Congress spend to buy vaccine for free shots, and who should get them? (2) How far should the federal government move into the picture to insure equitable allocation?

One of the proposals—this even got through the Senate—was to offer unlimited money to the states, which in turn could give free shots to any persons or group of persons under age 20. President Eisenhower's idea—which he urged on Congress several times—was simply to insure that no person in need of the vaccine would go without it for financial reasons. Eventually his view prevailed, and the states now are drawing on a $30 million fund. This law expires next February 15.

As weeks passed, there was less and less enthusiasm for setting up a federal allocation system, which Secretary Hobby and Surgeon General Scheele repeatedly told Congress wasn't needed. Consequently, when the National Foundation announced it had all the vaccine it needed for its program, a voluntary allocation plan was put in effect. The plan has the support and cooperation of physicians, pharmacists, drug manufacturers, and the state health officers. The Department of Health, Education, and Welfare is the liaison between the pharmaceutical houses and the states, dividing the vaccine on the basis of the number of unvaccinated persons in the eligible age groups.

U. S. Savings Bonds have been sold since March 1, 1935. The investing public called them "baby bonds" until the E bond was introduced as the Defense Savings Bond on May 1, 1941. Today over $38 billion in series E and H Savings Bonds are owned by around 45 million individuals in this country.

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1. Rosenberg, S. and Oster, K. A., "Gelatine in the Treatment of Brittle Nails," *Conn. State Med. J.* **19**:171-179, March 1955.
2. Tyson, T. L., *J. Invest. Dermat.* **14**:323, May 1950.

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Trudeau Society Scientific Meeting

The Kansas Trudeau Society will sponsor an all-day scientific session at the Hotel Kansan, Topeka, on Thursday, September 29. A short period of time after the morning program will be devoted to a business meeting, after which there will be a luncheon. The day will be concluded with a joint dinner session with the Kansas Tuberculosis and Health Association.

Dr. C. Frederick Kittle, University of Kansas School of Medicine, will be chairman of the morning session, beginning at 9:00 o'clock. Speakers will be Dr. Alfred M. Tocker, Wichita; Dr. Hector W. Benoit, Jr., Kansas City, Missouri; Dr. Frank A. Mantz, Jr., University of Kansas School of Medicine; Dr. Morgan Berthrong, Colorado Springs; Dr. Robert M. Brooker, Dr. George Zubowicz, and Dr. Andre Baude, Topeka.

Dr. Charles Pokorny, Halstead, president of the organization, will preside at the business meeting. Dr. Monti L. Belot, Lawrence, will be chairman of the luncheon meeting.

In the afternoon Dr. Ann Pollak, University of Kansas School of Medicine, will be chairman. Dr. Joseph D. Aronson, of the University of Pennsylvania, will speak on "The Role of BCG Vaccination in the Control of Tuberculosis," and Dr. David B. Radner, Chicago Medical School, will discuss "Tuberculosis among BCG Vaccinated Medical Students." A clinical and x-ray conference will follow.

Dr. Ralph I. Canuteson, Lawrence, will preside at the dinner session, and Dr. Joseph B. Stocklen, Cleveland, will deliver an address, "The Changing Order in the Field of Health."

Research Grants Renewed

Several grants to members of the staff of the department of pathology and oncology at the University of Kansas Medical Center have recently been renewed, covering a total of $53,650 for various projects.

Dr. J. David Robertson has received a grant of $8,150 from the United States Public Health Service for studies of the ultrastructure of the synapse. From the same source Dr. Harold Edelhoch has received $6,500 for studying non-specific factors in macromolecular interactions, and Dr. H. Adrain Stahl has received $6,000 for research on vacuum untraviolet microspectrophotometry.

Dr. Ann Pollak and Dr. Victor Buhler have a renewal of a grant of $7,000 for their study on the pathogenicity of cultural characteristics and antibiotic sensitivity of atypical acid-fast organisms.

The Atomic Energy Commission has granted the department $25,000 for cytochemical studies of irradiation ischemia and chemical agents on mammalian tissues. That project is supervised by Dr. Max Berenbom.

Dr. Joseph F. Miglairese, working under a grant from the American Cancer Society, received a renewal of his research fellowship, guided by Dr. Robert E. Stowell and Dr. Chauncey G. Bly.

Oklahoma City Clinical Conference

The Oklahoma City Clinical Society, organized in 1930, will hold its 25th annual four-day conference, October 24-27, and is extending an invitation to attend to all members of the Kansas Medical Society. Headquarters will be at the Biltmore Hotel, Oklahoma City.

The program will include presentations by 16 distinguished guest speakers, listed in an advertisement on Page 523 of this issue. Dr. Elmer Hess, president of the American Medical Association, will give the banquet address on October 24. Daily luncheon question and answer sessions and a clinicopathologic conference will also be features. Social events will include dinner meetings, a dinner dance, and a stag smoker.

Urologic Society Programs

The Kansas City Urologic Society announces programs for seven meetings to be held during the 1955-1956 season at the Pine Room, Union Station, Kansas City, Missouri. Following is the list: September 28, "Kidney Transplants," Dr. R. W. Stockton and Dr. George Aaron, Kansas City, Missouri; October 26, "Uretero-Pelvic Obstructions," Dr. Walter Mau and Dr. James A. McClure, Topeka; November 30, "Experience with the Johanson Procedure," Dr. James Cope, Columbia, Missouri, and Dr. Robert B. Bristow, St. Joseph, Missouri; January 25, "Hemoglobinuric Nephrosis," Dr. Lawrence C. Johnson, Kansas City, Missouri, and Dr. Herbert Warres, St. Joseph, Missouri; February 22, "Tuberculosis of the Kidney," Dr. Ronald W. Stitt, Kansas City, and Dr. Ira T. Smith, Kansas City, Missouri; March 28, guest speaker for urological seminar; April 25, "Endoscopic Extraction of Ureteral Calculi," Dr. James F. O'Malley and Dr. Stoughton F. White, Kansas City, Missouri.

The ninth clinical meeting of the A.M.A. will be held in Boston, November 29 through December 2, 1955. Hotel reservations may be made through Chairman, A.M.A. Housing Committee, 80 Federal Street, Boston 10, Massachusetts.

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Trypsin in the Treatment of Venous Thrombosis

Victor M. Eddy, M.D.
Kansas City, Kansas

During the last 10 years, accounts concerning the use of trypsin as a therapeutic agent have been seen in the literature with increasing frequency. Over this period, trypsin has been evaluated in many disease entities with venous thrombosis receiving considerable attention. Though much work has been done and much accomplished in understanding the nature of this drug as a therapeutic agent, investigators are not in agreement on its effect on venous thrombosis.

Efforts to understand the action of trypsin in the treatment of venous thrombosis have implicated it in the various mechanisms of clot formation, clot lysis, formation of thrombi, and basic enzymatic mechanisms, many aspects of which are still poorly understood. Conflicting terminology and experimental results have complicated the picture and have led to a considerable amount of confusion concerning its effectiveness. Therefore, an attempt will be made in this paper to survey the background and the experimental and clinical impressions of those interested in this subject. Finally, the possible future use of trypsin in venous thrombosis will be presented.

EARLY CLINICAL AND EXPERIMENTAL INVESTIGATION

Trypsin was known as early as 1836[48] and was given its name "trypsin" by Khune in 1867.[30] A crude extract of the pancreas was used as the source of trypsin in the early 1900's when Lewis injected the extract subcutaneously in an area of diseased tissue. He observed that this extract seemed to cause a severe reaction with the diseased tissue while no reaction seemed to take place in the surrounding healthy tissue.

Bätzner[3] used the extract topically and intravenously on soft tissue tubercular abscesses, and tuberculosis of the bones, joints, and lymph nodes.

It has also been used to some extent in attempts to dissolve fibrinous adhesions of the lung and thick, tenacious bronchial secretions.

Ever since the days of the earliest descriptions of enzymes and the clotting mechanisms of the blood, trypsin has been closely associated with blood clotting. Consequently, a wide variety of terms arose to describe the association of trypsin to the normally occurring lytic factor of the blood. Such terms as "serum trypsin," "serum trypsin inhibitor," "serum protease," and "soybean trypsin inhibitor," are all frequently seen and implicate trypsin in the clotting mechanism.

Early experimental investigation of the so-called "lytic system" of the blood has given some information on the action of trypsin as well as to the reasons for associating trypsin to this factor in the past.

In 1838, it was observed that fibrin clots would lyse spontaneously.[10] A similar action was observed in cases of sudden death[42] where blood was found to be incoagulable. This was also found in cases of peptone and hepatic shock[43] and in patients with hemolytic staphylococcus infections.[57] When efforts were made to identify the nature of the fibrinolytic substance, it was subsequently found that serum with chloroform added accelerated fibrin clot lysis.[9] It was thought by Dastre[9] that this represented the presence of an enzyme in serum which chloroform activated and which he termed "fibrinolysin." This action was also found to be a property of trypsin, but the whole situation was further complicated by finding that both substances would also clot oxalated blood.[11, 23, 40, 43]

In 1893 and 1897, Hildebrant and Hahn and others demonstrated that normal serum could inhibit the proteolytic activity of trypsin.[5, 21, 22, 35] Others obtained a pancreatic extract which would also inhibit the lytic action of trypsin.[59] Subsequently, numerous investigators were able to find antitryptic and antifibrinolytic factors in many tissues and in the albumin fraction of serum. These substances were subsequently called "serum trypsin" and "serum trypsin inhibitors" by several investigators.[24, 44, 51]

In the early 1930's, investigators began to suspect that other enzymes might be responsible for these actions. It was found by Mole[41] that the lytic factor was present even after the pancreas was removed. Other works substantiated that, although the lytic factor of normal serum closely resembled trypsin, it was apparently another enzyme which was responsible for these actions.[13, 29, 54]

In 1945, Christensen and McLeod[6] proposed the terms "plasmin" for the lytic factor, "plasminogen" for its precursor, and "antiplasmin" for its inhibitor. They also suggested that "plasmin" should replace the previous terms of "serum trypsin," "serum protease," "fibrinolysin," "serum tryptase," and "thrombolysin." They further stated that the effects of lysis,

This is one of 11 theses, written by fourth year students at the University of Kansas School of Medicine, selected for publication by the Editorial Board from a group judged to be the best by the faculty at the school. Dr. Eddy is now serving his internship at the University of Kansas Medical Center.

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such as occurred in sudden death, peptone and hepatic shock, chloroform, and stress were also due to plasmin activity. These workers also felt that "antiplasmin" should be substituted for the terms "crystalline antitrypsin" and its activity analogous to that observed with soybean trypsin inhibitor, and heparin. This terminology has been re-emphasized in the transactions of the first conference on blood clotting and allied problems.[4]

Various attempts have been made to explain the apparent dual role of trypsin and the related enzyme plasmin in clot formation and clot lysis. It was initially thought that their action was against the antitrypsin or antiplasmin factor. Others postulated that the crude or impure trypsin, used in early experiments, contained enough Ca^{++} to account for its ability to clot oxalated plasma.[39] Some thought that by enzymatic action trypsin would hydrolize fibrinogen to thrombin.[60] Lenggenhagen[35] thought that the clotting ability could not be demonstrated in serum which was in motion, and that trypsin and plasmin were capable of obtaining Ca^{++} from another source, such as protein bound calcium, which was necessary for the clotting action of these substances.

Another group, accepting the dual role of trypsin, attempted to show that plasmin or a similar proteolytic enzyme was a normal component of the clotting mechanism. Douglas and Colebrook[11] tended toward this when they showed that small amounts of trypsin accelerated clotting whereas large amounts seemed to cause lysis. This has been confirmed by Ferguson and Erickson[16] and was further advanced by Eagle and Harris,[13] who felt both processes went on simultaneously. They further showed that the total amount of thrombin formed with trypsin amounted to only one-fifth to one-half that formed by prothrombin. This has indicated that trypsin acts in the clotting mechanism at the prothrombin level rather that at the thrombin-fibrinogen level. Several others have supported this work.[8, 55]

In more recent years, there appears to be a trend toward favoring the theory that a normally occurring proteolytic enzyme "plasmin," similar to trypsin, is a component of the blood clotting mechanism.[14, 15, 35] More recently, efforts have been directed toward showing plasmin to be a normal component of thromboplastin. This theory will be offered in some detail later.

PHARMACOLOGY AND PHYSIOLOGY

Distribution: It is generally accepted that trypsin is present in an inactive form in the pancreas of the normal individual and is present in the active state in the intestine and feces. The exact site at which the transformation from the inactive to the active state occurs is still argued, but it is generally regarded to be at some point in the pancreatic duct or small intestine. Trypsin is usually considered to be excluded from the circulation in the normal individual, but some feel that it may gain access to this media in certain pathological states, such as acute or chronic pancreatitis.[1, 12] This has also been inferred, through the work of some who have investigated the incidence of vascular clotting, in cases of carcinoma of the body and tail of the pancreas.[53]

Various investigators have been able to demonstrate the presence of antitryptic, or more correct, antiplasmin substances in the extracts of different organs. Those tissues having the greatest antitryptic levels are the spleen,[58] the pancreas,[44] and the blood plasma and cells.[20, 55] Evidence of antitryptic activity in a wide variety of tissues has been used to explain the inability of trypsin to digest the gastrointestinal tract. This concept has also been used to explain the reaction observed in the early use of trypsin on diseased or dead tissue while the inhibitor apparently protected the healthy tissue.

Though trypsin is normally localized in distribution, it is possible that in certain pathological states it may gain access to the general circulation and may explain the hemorrhagic state which is generally associated with acute pancreatitis. Innerfield[27] has used an "antithrombin test" in the diagnosis of early or obscure pancreatitis and feels that this test demonstrates increased activity of the lytic system. However, he does not state that his test is evidence that trypsin is present in the circulation but rather some substance similar to it is stimulated or freed from its inhibitor in this disease. The substance is probably plasmin.

SITE AND MODE OF ACTION

I. *Clotting Mechanisms:* During its history, trypsin was implicated in several mechanisms which are important in considering its use in the treatment of venous thrombosis. This has been further complicated because the mechanisms of lysis and clotting are not fully understood either separately or in relation to one another.

Its site of action has been fairly well limited to the prothrombin level in the clotting mechanism, but whether its action is primarily lytic, coagulative, or some of both is purely speculative. These three different ideas will be briefly summarized.

Those workers who feel that the ability of trypsin to clot oxalated blood is a primary action, state that the action is at the prothrombin level. Trypsin then exerts its action by combining with prothrombin or accelerating its conversion to thrombin. (Figure 1). Support of this view has been reported by several workers,[13, 53, 54] and additional support may be inferred from Taylor, Overman, and Wright,[56] who

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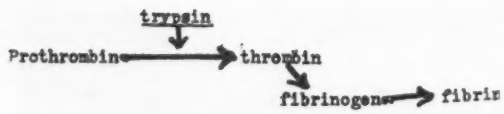

Figure 1

state that the use of coumarin derivatives will inhibit the clotting effect of trypsin.

Another group apparently feels that trypsin is primarily a lytic factor, and they fix the site of its action either on the so-called "lytic system" of the blood or directly on the various factors of the clotting mechanism (Figure 2). This concept, that trypsin enters into the plasmin system, has been supported by Lewis and Ferguson,[36] Peck,[47] Agress,[2] and Innerfield.[28] The direct action of lysing prothrombin, fibrinogen, and fibrin has been advocated by Roettig[50] and Madden,[37] but seems to place the primary site of action below the prothrombin level. This, however, may well be the secondary site of action.

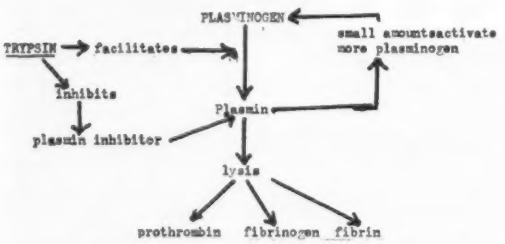

Figure 2. Adapted from Kochlaty, Ellis, and Jensen.[31]

Finally, there are those who endeavor to explain both the lysis and clotting as primary actions of trypsin. This has come about through inference that since both actions are prone to occur, a proteolytic enzyme is probably a normal component of the clotting mechanism. Since, however, trypsin closely resembles this enzyme (plasmin), its primary action is probably one of influencing blood clotting. Certain workers have gathered considerable evidence to advance this theory,[16, 18, 38, 56] and it appears to represent the present trend concerning the primary action of trypsin.

The advocates of this theory feel that thromboplastin is composed of a lipid-enzyme complex. The lipid has the action of the enzyme inhibitor (antiplasmin), while the active component of thromboplastin is the enzyme (plasmin). It is proposed that trypsin primarily interferes in the lipid enzyme complex, serving in effect to remove, or inhibit, the lipid portion of thromboplastin. By this mechanism, these workers feel that high levels of trypsin are necessary to abolish the inhibitor before a sufficient amount of trypsin will be present to exert its secondary lytic effect on the other clotting mechanisms such as fibrinogen, prothrombin, and fibrin. Clinical and experimental evidence seems to bear this out. Work with anticoagulants, heparin and coumarin derivatives, has been shown to inhibit the clotting action of trypsin, and therefore some have advocated their use in the form of an adjuvant to therapy with trypsin.

It has also been supported by finding that soybean trypsin inhibitor and antiplasmin extracts from various tissues can cause coagulation as well as inhibit the lytic action of trypsin. This mechanism may also serve to explain the phenomenon of clotting followed by lysis which is observed in vitro, as well as the difference in effects produced by large and small doses of trypsin. And, finally, it may be used to explain the apparent ineffectiveness of trypsin in lysing clots in vivo. That is, not until a high enough level is reached to overcome the inhibitor does lysis occur, and this level is sufficient to cause lysis not only of fibrin but also other proteins of the serum in such a rapid manner that shock and death follow.

This concept has been diagrammed in Figure 3. Whether Ca^{++} has been excluded from the mechanism of clotting by this theory still poses somewhat of a problem. Some investigators feel that more pure trypsin would exclude it, while others feel that the enzyme is capable of obtaining Ca^{++} from some other source (protein bound Ca^{++}), still making Ca^{++} and tissue factors necessary for clotting.

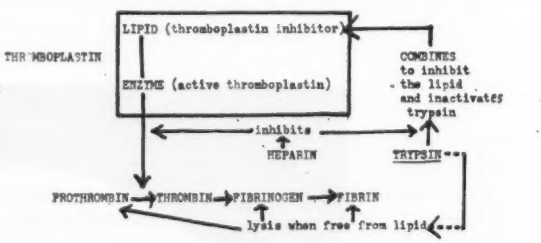

Figure 3.

II. *On Preformed Thrombi in Vivo:* The mechanism involved in the production of thrombi, like blood clotting, it not well understood. However, the clotting mechanism is regarded as necessary at some point in the formation of thrombi and has long been implicated as one of the various etiological factors of intravenous thrombosis.

Efforts to establish the effect of trypsin on thrombi produced in vivo have largely been done by introducing thrombin into the veins and arteries of animals and studying the effect of trypsin on the thrombi produced. Opinions on the effectiveness of trypsin on these preformed thrombi are varied. Some investigators feel that the thrombi are definitely lysed.

Meat...

and Biologic Facts of Protein Metabolism

The classical work of Cannon and his associates* in the field of protein metabolism has contributed significantly to our knowledge of the biologic utilization of protein. It has established that the dietary absence of a single amino acid quickly changes the direction of metabolic activity from anabolism to catabolism. Apparently all the nonessential amino acids play some part in sparing the essential amino acids, and all may be regarded as indispensable for optimal nutrition. It has been suggested "that for maximal tissue-utilization of amino acids at least twenty per cent of the total dietary nitrogen should come from other sources than essential amino acids."

In undernourished subjects the maintenance requirement for each essential amino acid is much greater—two to almost five times greater—than in healthy subjects.

Although an optimal caloric intake facilitates optimal utilization of amino acids, a reducing regimen need not curtail full utilization of these nutrients. It has been shown that a useful degree of amino acid utilization can be attained with caloric intake considerably below the optimal.

Minerals appear to be important in the process of amino acid metabolism. Evidence indicates that either phosphate or potassium deficiency might adversely influence amino acid utilization. Absence of either ion from experimental depletion rations leads to depression of appetite and slowing of the processes of protein repletion.

B complex vitamins also affect the metabolism of proteins and amino acids. For example, rats fed a high protein diet require a high intake of B complex vitamins in order to maintain normal growth rates. Omission from the ration of any one of these vitamins (riboflavin, thiamine, pyridoxine, or pantothenate) is accompanied, in varying degrees, by lower food consumption and slower weight gain.

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*Cannon, P. R.; Frazier, L. E., and Hughes, R. H.: Factors Influencing Amino Acid Utilization in Tissue Protein Synthesis, in Symposium on Protein Metabolism, New York, The National Vitamin Foundation, Inc., 1954, pp. 55-90.

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Others believe that the thrombus is altered in such a manner that complete occlusion will not occur. Still others believe that trypsin has no effect on thrombi produced in this manner.

Curiously enough, complications of thrombosis at the infusion site have been experienced in many cases, and a few investigators report instances of generalized intravascular thrombosis following intravenous infusion of trypsin. This action then appears to closely parallel that which occurs in vitro.

Innerfield, Angrist, and Schwartz[25] felt that lysis of thrombi in animals could only be demonstrated at levels which also produce shock. Their conception was that a high enough serum level of trypsin to lyse could not be achieved until the excess and rapidly formed inhibitor was inactivated by combination with trypsin. Only then could trypsin exert its lytic action on the thrombi.

Laufman and Roach[34] used trypsin both before and after producing the thrombus and found that the thrombus could be prevented if treatment was started before the thrombus was produced; but, when used after the thrombus was present, trypsin had very little lytic effect.

Agress and others[2] used intravenous trypsin in experimental coronary thrombosis in dogs. Their conclusion was that there may be some lytic action on the thrombus as trypsin seemed to prevent the complete occlusion which was observed in control dogs.

Tagnon[54] and Taylor, Overman, and Wright,[56] working with rabbits, found that trypsin could cause massive intravenous thrombosis. In the case of Tagnon, the rate of infusion was cited as the immediate cause. These workers state the trypsin given intravenously in 10 to 15 seconds resulted in a clinical picture of shock and death of all animals. Autopsy showing intravenous thrombi as the cause was found in most instances. When rabbits were given the same or larger dose, but over a longer period (one-fourth to one hour), no deaths occurred.

On the contrary, Taylor *et al.* felt that rapid administration of large doses could cause shock, but that a slower rate of infusion seemed to increase the instance of infusion site thrombosis. In their series of 10 rabbits, they report a mortality of 40 per cent with a 35 per cent incidence of local thrombosis at the infusion site. They noted no thrombolytic effect and in some cases thought that there was propagation of the primary thrombus. These workers further state that 90 per cent of the animals dying in early infusion showed intraventricular thrombosis, thrombosis of large veins and arteries, and pulmonary and myocardial hemorrhage.

Dragstedt and Wells,[12] Silva,[49] and Innerfield[26] have stated that the picture of shock which can be produced by trypsin closely resembles anaphylactic shock and the shock occurring in acute pancreatitis. Dragstedt and others state that the liver in such animals shows an increase in the histamine content and postulate that trypsin or proteolytic enzymes may play a role in histamine release. In their studies, they could prevent the shock with antihistaminics. Innerfield postulated that the shock was the result of digestive products produced by lysis of all components of the clotting mechanism. The preceding work may have elucidated the mechanism responsible for the shock produced by trypsin.

FATE AND EXCRETION

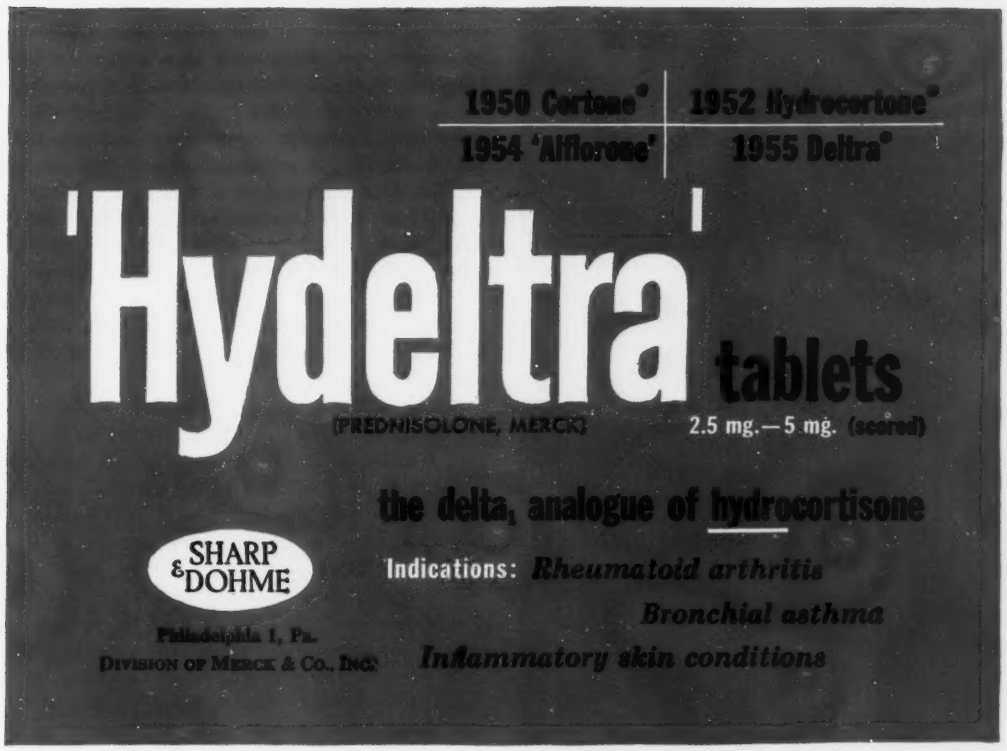
Most observers believe that trypsin is inactivated quite rapidly by combination with its inhibitor. Kunitz[32] states that approximately 98 to 99 per cent of the administered trypsin, regardless of dose, became bound to the inhibitor to form a strongly stable substance. Northrop[45] also showed that inhibition and inactivation were rapid. In addition, he found that combination in acid solution would not render trypsin completely inactive as it could be dissociated quite easily, resulting in active trypsin. He further states that if the combination were held at a pH of 7.0 for a short period that the enzyme would become permanently inactivated, probably through a digestive action of other enzymes.

DURATION OF EFFECTIVENESS

The stability of trypsin appears to be shortened when mixed with saline in preparation for intravenous use. Innerfield[25] states that 40 to 50 per cent of the lytic activity is lost in the first three hours.

From experimental and clinical evidence, trypsin may be considered to have a relatively-short duration of effectiveness. Because its use has been limited and conflicting results have been obtained regarding its effect on thrombi, recent efforts have been directed toward achieving only an adequate serum level with which clinical improvement can be noted. As will become more evident later, clinical improvement does not necessarily indicate thrombus changes occur and may mean only a subsidence of the symptoms produced by the thrombus.

Reports indicate that clinical improvement may precede any detectable laboratory changes by as much as one to four days after starting treatment.[25] Laboratory effects may be detected by the fourth day[34] and usually return to normal on or before the eighth day after starting treatment.[17] Innerfield's work with dogs showed a return of laboratory results to normal in the first 14 to 18 hours.[26] Some investigators found that changes produced in the thrombus, which are occasionally seen several weeks after treatment, indicate a longer duration of action of trypsin. It has been postulated that this may come



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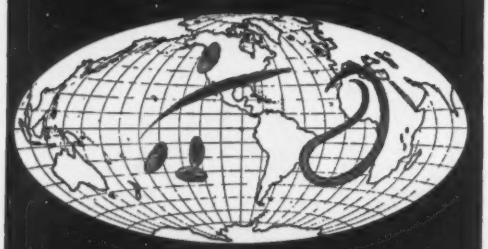

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about through activation of "another proteolytic system." However, if past experiments concerning the amount and distribution of a trypsin inhibitor are valid, then such a long action of trypsin could not be considered likely.

Recently, a preparation of trypsin and sesame oil was developed for intramuscular use. The effective duration of this preparation has not been conclusively studied but may be somewhat longer than trypsin given intravenously. This is implied in the work of Innerfield[28] who used intramuscular trypsin in certain cases of chronic thrombophlebitis at weekly or semi-weekly intervals. He found that recurrence of symptoms appeared in three to five days after therapy had been discontinued.

When trypsin is given intravenously, clinical improvement is usually noted before effects on the clotting mechanism can be detected in the laboratory. Since treatment is directed toward obtaining a trypsin level which will produce clinical improvement, it usually is administered only over a period of about four days. Laboratory effects can be noted from approximately four to eight days after treatment. The duration of effect might then be compared to that of intramuscular trypsin. Experiments similar to those done with the intravenous route and timing the return of the clotting system to a normal state would possibly be of some value.

RECENT CLINICAL INVESTIGATION

Types and Cases Treated. Trypsin has been used in a variety of disease entities. In an effort to determine the effect of trypsin on venous thrombosis, attempt has been made to isolate from the wide variety of diseases reported those cases of venous thrombosis which have been treated with trypsin. These have been listed in Table 1. Three hundred fifty-seven studies have been obtained in this manner which, for the sake of brevity, could be classed as acute cases of chronic thrombophlebitis and phlebothrombosis. The location of the thrombus has in most cases reported been in the lower extremity, with other loci cited in a few instances.

Routes and Dosage. Recently there has been some disagreement as to the dose of trypsin which should be administered by the intravenous route. This difference of opinion concerns whether trypsin should be used to lyse thrombi or to lessen the symptoms and complications produced by the thrombus.

Some authorities[25, 34] advocate the use of 100,000 to 200,000 units of crystalline trypsin as a thrombolytic dose. This dose is mixed with 250 cc. of normal saline shortly prior to treatment. Infusion is started in a large cubital vein with the arm slightly elevated and using a Number 23 gauge needle. The rate of infusion is regulated at a constant 25-35 drops a minute. This dose is repeated daily for four

consecutive days. The series may be repeated again after two to four days.

Reports and clinical evidence, however, seem to show a more dramatic anti-inflammatory effect than thrombolytic effect, which has caused some to decrease the dose.[17] It has been found that an initial dose of 10,000 units crystalline trypsin in 250 cc. of normal saline, given in the same manner, and increased daily by increments of 10,000 units daily to a total of 50,000 units, will give the same anti-inflammatory effects produced by the larger dose.

Since the intravenous route is accompanied by several distressing side effects and is inconvenient and uncomfortable for the patient, the intramuscular route has been stressed more recently.

Intramuscular trypsin in oil has been supplied under the trade name of Parenzyme in lots containing 5 mg. of trypsin per cc. (approximately 80,000 units). The dose advocated is from 2.5 to 5.0 mg. by deep intragluteal injections daily for four consecutive days. This route of administration has made possible ambulatory treatment following the remission of the acute or chronic illness.[28]

Investigators state that intramuscular treatment for four consecutive days is usually adequate to produce clinical improvement. Innerfield[4] followed the initial four days with 1.0 cc. daily until the patient was improved and ambulatory. He then followed that with five to 13 weeks of weekly or semi-weekly doses to prevent recurrence.

Correctives. Certain side effects have been frequently noted to accompany intravenous infusions of trypsin solutions. Precautions as to the technique of infusion and the use of certain medications in conjunction with trypsin seem to have eliminated most of these effects.

The incidence of infusion site thrombosis may be lessened with the use of a large vein and a Number 23 gauge needle to easily maintain a constant rate of flow of 25-35 drops per minute.

Pain, induration at the infusion site, and local inflammatory reactions may be diminished with slight elevation of the arm and the use of antihistaminics, such as Benadryl, 50 mg. by mouth, or Chlor-trimeton with 25 mg. in the infusion mixture.

Fisher and Wilensky[17] incorporated 25 cc. of Sorenson's phosphate buffer in the mixture to obtain a buffering effect and render the solution more physiological.

The complication of intravascular thrombosis has not been described in cases where the intramuscular route has been used; but, if previous work indicating a histamine release from trypsin therapy is correct, antihistaminics may also be needed when the intramuscular route of administration is used. However, slow absorption may not release histamine in large amounts as seen in intravenous therapy.

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TABLE I

Investigator	*Number Patients*	*No. and Type of Cases Treated*		*How Treated*	*Clinical Effect*
Laufman[24]	41	30	Acute thrombophlebitis	I.V.	Marked relief of symptoms in 3 days.
		11	Chronic thrombophlebitis	I.V.	Decreased pain, swelling, and tenderness.
Fisher and Wilensky[17]	8	8	Thrombophlebitis not responding to other therapy	I.V.	Asymptomatic in 2-3 days.
	37	16	Saddle thrombi	I.V.	No response.
		13	Cerebral thrombi	I.V.	No response.
		8	Pulmonary infarcts	I.V.	All survived.
	80	80	Acute thrombophlebitis	I.M.	75 of 80 with decreased pain, calf tenderness, edema, temperature, and sedimentation rate. Later decreased size of thrombi, incidence of pulmonary infarcts, and post phlebitic syndrome.
Golden and Herkimer[19]	8	8	Acute thrombophlebitis	I.M.	Asymptomatic in 12 to 24 hours.
Laufman and Roach[24]	30	10	Acute thrombophlebitis	I.V.	Acute symptoms gone in 48 hours.
		20	Chronic Thrombophlebitis	I.V.	Little effect.
Innerfield, Angrist, and Schwartz[26]	114	74	Acute thrombophlebitis	I.V.	Decreased size of thrombi in 24 to 48 hours. Completely gone in 2 weeks. No response in 3 patients.
		4	Chronic thrombophlebitis	I.V.	Reduction of edema in 24 to 48 hours.
		10	Phlebothrombosis	I.V.	Reduction of edema in 24 to 48 hours.
		12	Post operative thrombophlebitis	I.V.	Acute inflammatory reaction gone in 48 hours.
		2	Thrombosis of abdominal wall varicosis	I.V.	Thrombi gone in 4 weeks.
		12	Central retinal vein thrombosis	I.V.	Subsidence of edema in 24 to 48 hours.
Innerfield[28]	18	18	Selected, therapy resistant, chronic recurrent thrombophlebitis	I.M.	Clot slowly subsided. Circulation returned. Edema improved. Recurrence upon stopping injections.
Peck[27]	1	1	Chronic thrombophlebitis	I.V.	No recurrence using Hydergine and elastic stockings over 6-months period.

needed to combat the thrombotic effects produced by trypsin. However, the use of these agents as correctives has not been described in the literature.

CLINICAL EFFECTS

There appears to be a trend away from the idea of expecting trypsin to alter a thrombus or lyse thrombi by proteolytic action. However, some investigators still feel that at least the size of a palpable thrombus may be altered, and this possible proteolytic effect cannot be entirely eliminated at present.

Innerfield[25] states that thrombi will decrease in size in the first 24 to 48 hours after treatment and disappear completely in approximately two weeks. In his later studies,[28] he states that the thrombi slowly disappear and circulation eventually returns to the thrombosed vein segment. However, he states that edema did not completely resolve in every case, but in most instances it improved considerably. Innerfield's work has been supported by Fisher and Welensky[17] who found that approximately 80 per cent of the palpable thrombi resolved in the first 24 hours of treatment. In addition, Golden and Herkimer[19] found that there was a striking resolution of the thrombus. Furthermore, Agress[2] was satisfied that thrombi could be altered enough to prevent complete occlusion. His work was on experimentally produced thrombi in dogs.

Laufman and Roach[24] feel that their experience has not shown trypsin to cause any exceptional changes in the state of the thrombus. They did think that the reduction of inflammation was much more striking in the studies than any effect on the thrombosis. In efforts to control their studies, these men in-

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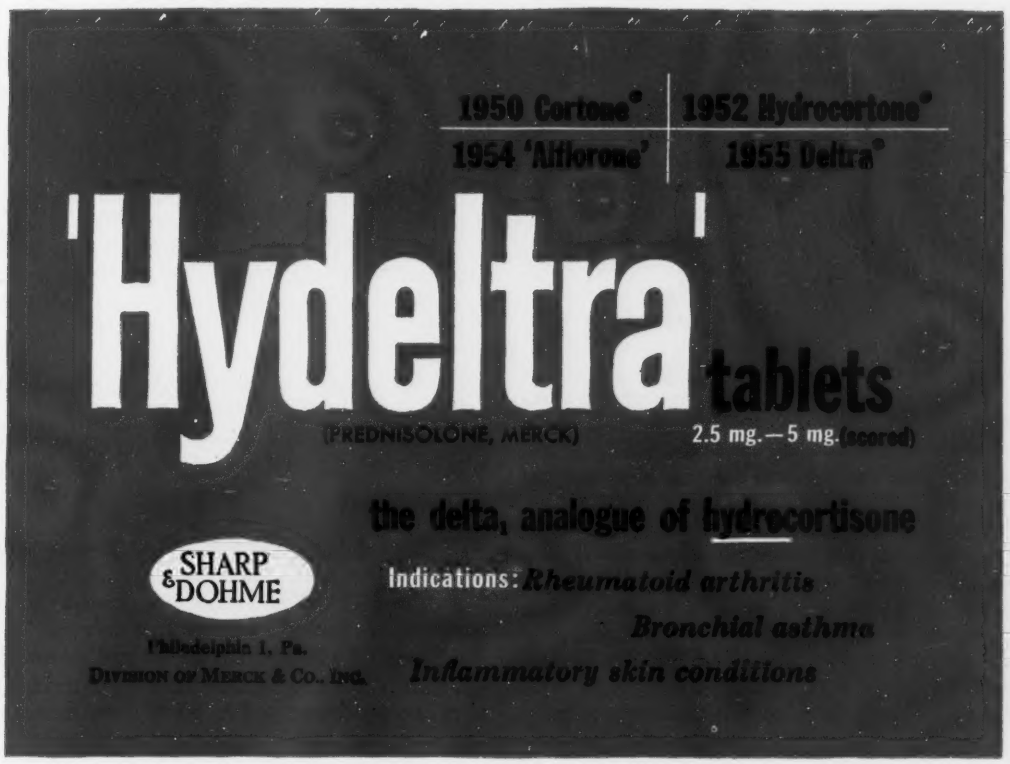


stituted a three-day rest period prior to treatment. This effort was directed toward determining the effect of compulsory rest, elastic stockings, and elevation of the extremity on the state of the thrombus. They found no appreciable difference between patients treated with trypsin and controls. They do state, however, that patients who had secondary inflammation or infection superimposed on chronic thrombophlebitis did show more rapid improvement of the secondary lesions under trypsin therapy. Peck[47] came to the same conclusion.

Taylor, Overman, and Wright[56] state that since intravenous trypsin can cause thrombosis and, in some instances, cause propagation of a preformed thrombi produced in the ear veins of rabbits, trypsin should not be used as a therapeutic agent. They also feel that local phlebitis is easily treated by conventional means with satisfactory results, thus avoiding the dangers of trypsin therapy.

From reports of clinical use of trypsin in venous thrombosis, it is evident that case studies with adequate controls have been limited. The value of treatment with trypsin is questionable, especially if lysis of the thrombus is expected.

The greatest cause for objection to the use of intravenous trypsin in venous thrombosis is that trypsin is not thrombolytic with the present advocated dose. However, all using trypsin for this purpose agree that trypsin can cause rapid subsidence of coexistent inflammation, ulceration, and secondary infection.

Numerous reports state that the various signs and symptoms of venous thrombosis, such as pain, edema, tenderness, and Homan's sign, subside dramatically with trypsin therapy. Conventional treatment of these symptoms usually takes from six to 12 days to reduce the effects where trypsin can do it in one to three days (Table I).

This effect appears to be equally well produced with either the 250,000 unit dose or 50,000 unit intravenous dose or if the 5.0 mg. intramuscular dose is used. This feature alone is believed by some to be justification of the use of trypsin.

The incidence of success of the anti-inflammatory action in the 337 cases gathered from reports shows that approximately 82 per cent of the symptoms in cases of acute thrombophlebitis were absent in one to three days, and the same was true in 93 per cent of patients with chronic thrombophlebitis.

Reports of thrombolytic effects produced by trypsin cannot be disregarded altogether at present. Though the series of cases presented here is relatively small and control cases are at a minimum, there appears to be some significance to the incidence of size decrease of palpable thrombi. The incidence reported is shown to be from approximately 32 to 27 per cent in both acute and chronic thrombophlebitis (Table II). Naturally, the incidence of size decrease of the thrombus depends upon its location and availability either to visual or manual examination and does not appear to be an adequate estimation of thrombolytic effect. Contrary to what one would expect to find, if the evidence given by Agress is supported, there appears to be less thrombolytic effect in acute than in chronic cases of thrombophlebitis.

It would appear that a trial of conventional treatment might reduce the incidence of both the anti-inflammatory and thrombolytic effects of trypsin.

SIDE EFFECTS

Reports have indicated several undesirable and even severe reactions following the use of intravenous trypsin. These may be listed as objective and subjective.

Objective

1. Local thrombosis at the infusion site. Fisher and Wilensky[17] report the incidence at 0.7 per cent.

2. Allergic protein reaction. It has been stated that since trypsin is a low molecular weight protein, its allergenic potentialities are minimal. Fisher and Wilensky[17] investigated this aspect and found by intracutaneous testing that there was some correlation between the degree of reaction, the size of the dose, and a past history of allergy. They found that no reactions could be obtained with a dose of 50,000 units, but in patients with allergic history one-third showed reaction with the test to 200,000 units.

3. Purpura. Minor purpura was reported by Innerfield[25] with an experimental dose of 750,000 units of trypsin.

Subjective

Peck[47] listed the subjective reactions as immediate and latent. He states that these complaints usually accompany the first dose, are found only occasionally on the second dose, and rarely with the third. He states that the same sequence would occur with each series of treatments.

1. Immediate

a. Flushed face, warming sensation, feeling of well being occur frequently.

b. Sensation of suffocation lasting one to three minutes after the start of infusion is occasionally seen.

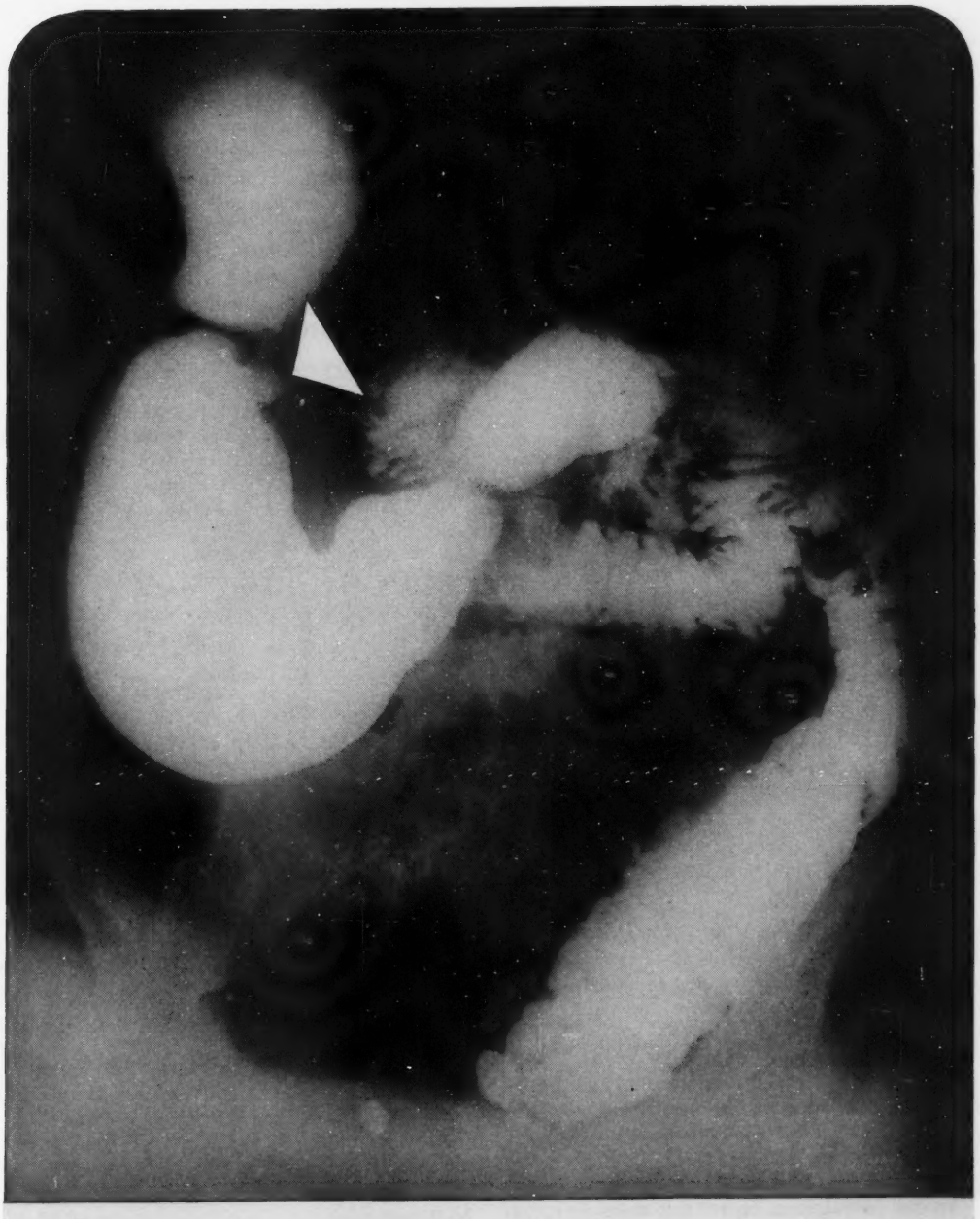
2. Latent

a. Chill, slight depression of blood pressure with or without temperature elevation.

b. Anorexia, nausea, abdominal cramps occur usually within two to six hours after infusion.

c. Vomiting and pain in the infused extremity.

Generally, most of these reactions are regarded as of minor significance as they are of short duration,



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controllable in most instances. Peck feels that none of the side effects he observed were an indication to stop therapy.

TABLE II

Acute thrombophlebitis	*No. treated*	*No. asymptomatic*	*Lytic effects*
	30	30	
	16	0	
	13	0	
	8	0	
	8	8	
	80	75	
	10	10	
	74	71	71
	12	12	
	12	12	
	263	218	71
Chronic thrombophlebitis	11	11	
	8	8	
	20	20	
	4	0	
	2	2	2
	18	18	18
	1	1	
	64	60	20
Phlebothrombosis	10	10	

Intramuscular therapy has been reported to be free of many of these side effects and therefore appears to be the treatment of choice. The side effects from intramuscular trypsin have been listed as local pain and tenderness at the side of injection in 15 per cent of the cases, and nodule formation has been reported to occur occasionally. Innerfield[28] states that he has not experienced systemic allergic manifestations with this method of treatment.

There have been no reports in the literature of fatality caused by either intravenous or intramuscular trypsin.

LABORATORY EFFECTS

Most investigators find minimal effects produced by trypsin on the clotting mechanism as shown by laboratory tests.

It has been reported that when trypsin is given by intravenous injection, one may expect a slight increase of the prothrombin time for about six days, a diminished total serum protein (mostly of the globulin fraction) which goes from 2.75 to 2.0 for four to eight days, a slight drop in fibrinogen, and a slight leukocytosis. The intramuscular route has been reported to cause a slight increase in the prothrombin time also.

Several investigators report that there is no appreciable effect on the complete blood count, hemoglobin, sedimentation rate, coagulation time, prothrombin time, hematocrit, BUN, serum glucose, urinalysis, serum fibrinogen, or electrocardiogram.[2, 34]

Precautions and contraindications. Since the effect of trypsin on the various systems is still not fully understood, it should not be inferred from the minimal effects noted in laboratory determinations or in the clinical effects that therapy with this agent is innocuous. Experiments show that overdosage may lead to death though it is likely that the fatal dose is several times the amount used for treatment.

Therapy is contraindicated in cases of congestive heart failure and severe anoxia, and cyanosis for methemoglobinemia has been described to occur as a result of a change in the oxygen carrying capacity of the trypsinized red blood cell.

Trypsin therapy is not advised in liver disease or hemorrhagic states, and Fisher and Wilensky[17] list renal insufficiency as a contraindication.

IMPRESSIONS AND CONCLUSION

The participation of trypsin in the clotting mechanism has been suspected for many years, but its mode of action is still unknown. Investigation of trypsin has intensified since Northrop, in 1932, obtained a relatively pure crystalline form.

For many years trypsin was considered as a normal proteolytic factor occurring in serum, but investigation has found that trypsin only resembles the proteolytic factor plasmin which is present in states of sudden death, stress, anxiety, burns, and trauma.

The mode of action of trypsin is still unknown, but several similar effects have been shown to occur in vitro, in vivo, and in its clinical use. The mechanism seems to be a primary clotting action followed by secondary lytic action. The site where trypsin exerts its effect is possibly at the thromboplastin level.

Clotting actions observed in vitro have also been observed in laboratory animals and in clinical trials with intravenous trypsin. Although the formation of vascular thrombi is not fully understood, it seems evident that the clotting mechanism takes part in thrombus formation. Lysis of thrombi with trypsin apparently is not as evident in human and animal studies as the in vitro demonstrations would seem to indicate. Postulating the presence of a large amount of a substance, free in the cells and serum, which will inhibit trypsin in vivo would appear to explain this discrepancy.

In recent years trypsin therapy has been directed toward the anti-inflammatory action rather than the thrombolytic action. This improvement may not only be seen as reduction of symptoms but also as shortening the course of superimposed inflammation, ulceration, and infection. The mechanism of this action is also thought to depend on the fibrinolytic action of trypsin. The action seems to be on the exudate as the lysis facilitates circulation and permits antibiotics to come into closer contract with infecting organisms. This action suggests that a high level of trypsin would be necessary if proteolysis of fibrin

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REFERENCE: 1. Robinson, R. C. V., *J.A.M.A.* 157:1300, April 9, 1955.

is to occur. This would appear to be necessary from investigations based on the lysis of venous thrombi.

The inability of trypsin to lyse thrombi is not accepted by all investigators. Some still feel that thrombi produced at the infusion site are due to impurities of the product (alpha or beta chymo-trypsin) or due to poor technique of administration. Investigations of the effect of trypsin on the forming thrombus lend some support to the possible usefulness of trypsin's proteolytic properties. In some instances, trypsin appeared to prevent extension of thrombi if treatment was instituted shortly after the thrombus was formed. It further seemed to prevent thrombi from forming if instituted before the thrombus formed. However, it has not been reported that this mode of treatment has been investigated clinically.

On the whole, clinical investigation has been limited and controls have been few. There is some encouragement from reported cases of chronic thrombophlebitis, which are refractory to other forms of therapy, having responded to treatment with trypsin.

At present the greatest asset of trypsin appears to be in its anti-inflammatory effect. In a large number of instances pain, edema, and discomfort are ameliorated in the first 24 to 48 hours, as compared to six to 12-day periods required for resolution by conventional treatment. Secondary infection and leg ulcerations also appear to clear promptly with trypsin.

Since intravenous trypsin is accompanied by several undesirable side effects, and hospitalization is necessary for treatment, more emphasis should probably be placed on intramuscular trypsin. Intramuscular trypsin has been reported to have fewer and milder side effects. Although allergic manifestations have been regarded as rare, they should be considered, especially when an allergic history is obtained and if the use of a large dose is contemplated.

Even though laboratory effects are noted to be of short duration and of minor importance, the laboratory should be utilized prior to therapy to determine bleeding tendencies or liver disease.

If proper precautions are kept in mind as to the dose, rate of administration, and correctives used, there do not appear to be any serious reactions from intravenous trypsin. However, the benefit obtained from this method of treatment appears to be no better than the more easily administered intramuscular form and is certainly less discomforting and dangerous for the patient.

Trypsin does not seem to fulfill the need for a thrombolytic agent which can be used in the treatment of venous thrombosis. Its value may lie only in lessening the acute symptoms of inflammation, infection, and ulcerations, and in affording earlier ambulation.

The indication for trypsin therapy in venous thrombosis, at present, appears to be in those cases of chronic thrombophlebitis which are refractory to trial with conventional management. It may also be indicated in the prophylactic treatment of postoperative venous thrombosis and in conjunction with heparin or dicumarol therapy.

The need for a better thrombolytic agent is still present. Perhaps the recent work on the isolation of plasmin by Clifton, Grossie, and Cannela[7] may be helpful. They have indicated that its thrombolytic effect surpasses trypsin. Sherry, Titchener, and Leonard[53] state that plasmin and streptokinase together have a much stronger lytic effect than either plasmin or trypsin alone.

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Most county medical societies hold no meetings during the summer months and begin their fall series of sessions in September. A good member always attends if possible.

THE KANSAS PRESS LOOKS AT MEDICINE

Editor's Note. In this section the JOURNAL *reproduces editorials relating to medicine which have appeared in the lay press. An effort is made to include both favorable and unfavorable comments, and the Editorial Board in no instance assumes responsibility for the opinions expressed.*

THE MEDICAL CUSHION GROWS

Here's a bit of good news: The American people are doing a pretty good job of voluntarily cushioning themselves against the financial impact of illness.

A survey made by the Health Insurance Council tells the story. Nearly two out of every three men, women and children in the United States are now covered by voluntary health insurance. Some 104,000,000 have insurance against hospital expense, 89,000,000 have surgical expense protection, and 50,000,000 have regular medical expense protection. . . .

Another striking fact is that since the beginning of 1941 the number of persons with hospital expense protection has multiplied nearly eight-and-one-half times.

Finally there is an important and very new development—major medical expense insurance, covering what is known as catastrophic illness. More than 2,200,000 people now have this protection—a jump of 83 per cent in a single year.

No one claims that the financial problems connected with illness are all solved. But the point is that we are making dramatic progress toward the goal—and we are doing it voluntarily and on our own hook, not because the government forces us to.—*Abilene Reflector-Chronicle, July 30, 1955.*

Small towns in need of a physician can find the answer to their problem by studying the plan used at McLouth. The story has been told over and over again in hundreds of publications and from many platforms. The people of the community provided offices and a home for a doctor on terms that allowed him to acquire ownership over a period of years. The story has recently been made into a film by Mosser-Wolfe and will be shown all over the nation by the American Medical Association. McLouth now has a well trained medical doctor living in the community and giving excellent service to the people. Many other communities have followed the pattern set by the people of McLouth. It is the prac-

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tical answer to the problem that comes, sooner or later, in every small community.—*McLouth Times, August 4, 1955.*

Crime and the Citizen

(This is another in a series of letters to the *News-Herald* from distinguished Kansans on the subject of sex criminals. The *News-Herald* invites all its readers to join in the discussion.—ED)

Thank you for the opportunity of seeing your editorial on sex criminals. The physicians of Kansas have been concerned as you and many others have been about these indefensible crimes. If there is anything the members of the Kansas Medical Society can conceivably do to prevent even one recurrence we want to do it.

Unfortunately, good intentions are not enough. The Legislative Council, I believe, has been charged with the duty of attacking this situation. Attempts will be made to recognize and control the criminal sexual deviate if possible before some outrage has occurred. Certainly, the psychiatrist must play a large part in this and I am sure those specialists in our Society are ready and anxious to help. Cooperation of doctors with lawyers, penologists and others concerned with this problem can be assured.

The press has made a tremendous contribution in bringing these cases frankly and honestly to the attention of the public. The press can be of further service by emphasizing the rarity of these occurrences and refusing to over-play the dramatic and prurient sides of the picture.

At present the stock phrase of the authorities that "known sex offenders are being investigated" has worried many people. Some apprehensive parents are led to believe that sex offenders capable of major crimes are frequent and well-known to the police. Recognized molesters of children should be kept under such surveillance or confinement that they have no opportunity to cause harm but it is doubtful if widespread drives against the minor sex deviate of only mildly anti-social attitudes would prevent many serious crimes. It is possible that laws regarding punishment and parole of this type of criminal are too lenient. Certainly the Legislative Council should answer this.

The situation calls for calm investigation by experts who know how these diseased minds work, by men who are familiar with the results of jail sentences, paroles, fines, and other punitive or correctional measures, by trained lawyers and law-makers and others working in response to an enlightened public, guided and informed by an alert and intelligent press.

It should be emphasized that these are the individual opinions of an internist with no particular training in psychiatry. I can, however, promise 100 per cent cooperation from the Kansas Medical Society.—*J. M. Porter, M.D., President, Kansas Medical Society, Concordia.—Hutchinson News-Herald, August 7, 1955.*

BOOK REVIEWS

Surgery of the Alimentary Tract, Volumes I, II, and III. By Richard T. Shackelford, M.D., assisted by Hammond J. Dugan, M.D. Published by W. B. Saunders Company, Philadelphia. 2575 pages, 1705 illustrations. Price $60.

Occasionally someone writes a truly monumental work on some medical subject, one which is accepted as authority and remains as a standard text for longer than most medical books are kept. Such a work was Bickham's *Operative Surgery,* published in 1924. A revision of this work was started by Callendar, but his untimely death prevented completion of the task. Dr. Shackelford has completed the re-writing (rather than only a revision) of that part having to do with the alimentary tract, and the three-volume set is a worthy successor of an illustrious "ancestor."

Instead of only a description of operative technique, there is an evaluation of the various procedures described (and most operations done on this system today are included) with reasons why they are good or inferior and a concise discussion to help in selecting the best procedures.

The format is pleasing in appearance and readability; the illustrations are excellent. Each volume has the index for all three volumes, which greatly facilitates finding desired material, and most of the "desired material" is contained in the books. This work should prove to be a popular and useful one for any surgeon doing gastrointestinal work.—*O.R.C.*

Saddle Block Anesthesia. By Ray T. Parmley, M.D. Published by Charles C Thomas, Springfield, Illinois. 58 pages, 9 illustrations. Price $2.50.

This is an excellent short review of a small part of spinal anesthesia. The foreword by Doctor Adriani is most appropriate in giving the reader a well written opinion on the status of spinal anesthesia in general. The rest of the book deals with technique, with the basic physiology and pharmacology adroitly interwoven, but minimal in amount.

A separate chapter of ten pages on uses in obstetrics tells some of the arguments for and against this technique. The final chapter deals with com-

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Nov. 7-9	GYNECOLOGY
Nov. 14-17	INTERNAL MEDICINE
Jan. 16-19	SURGERY
Jan. 23 & 24	CHEST DISEASES
Jan. 25 & 26	GASTROENTEROLOGY
Feb. 13-16	RADIOLOGY & RADIOACTIVE ISOTOPES
Feb. 27 & 28	TENTH ANNUAL HEART CONFERENCE
Mar. 7	DENTISTRY & MEDICINE
Mar. 12-14	PEDIATRICS
Mar. 15 & 16	HEMATOLOGY
Mar. 19 & 20	CLINICAL CARDIOLOGY
Apr. 9-13	OPHTHALMOLOGY & OTOLARYNGOLOGY
Apr. 16-18	ANESTHESIOLOGY
June 11-23	HISTOCHEMISTRY

Continuation Courses

Oct. 20-Apr. 19	GENERAL PRACTICE (Afternoon sessions, 3rd Thursday of each month)
Nov. 17-Mar. 15	SURGERY—OPERATIVE CLINICS (All-day program on 3rd Thursday of each month, except Jan.)
Nov. 29-Apr. 27	SIX MONTHS CIRCUIT COURSE Afternoon and evening sessions, one day each month, at each of the following centers: Concordia, Colby, Hays, Dodge City, Salina, Hutchinson, Winfield, Parsons, Atchison, Topeka and Emporia
Jan. 22-Mar. 25	ROENTGENOLOGICAL PHYSICS (Two-hour session on Sundays, time to be determined)

Correspondence Courses

Oct. 21-Apr. 20	INTERPRETATION OF ELECTROCARDIOGRAMS—
Apr. 20-Oct. 18	Course I (Twenty-six weekly lessons)
Nov. 24-May 24	INTERPRETATION OF ELECTROCARDIOGRAMS—
May 10-Nov. 8	Course II (Twenty-six weekly lessons —for those who have completed Course I)

For Allied Groups

Aug. 1-12	TUBERCULOSIS NURSING INSTITUTE
Nov. 21 & 22	OPERATING ROOM & CENTRAL SERVICE INSTITUTE
Jan. 9-11	MEDICAL TECHNOLOGY
Feb. 6-8	NURSING & NURSING EDUCATION
Feb. 24 & 25	HEARING & SPEECH CONFERENCE
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plications and warns the anesthetist of the ways they can be avoided.

This is a useful addition to the literature. It can be read easily in one night, and the "pearls" acquired will be well worth utilizing.—*E.L.F.*

ANNOUNCEMENTS

The 85th annual session of the Colorado State Medical Society will be held in Denver, September 20-23, with headquarters at the Shirley-Savoy Hotel. Guest speakers will be Dr. L. Henry Garland, San Francisco; Dr. Philip D. Wilson, New York; Dr. John C. Burch, Nashville; Dr. Charles Ragan, New York; Dr. James T. Priestley, Rochester, and Dr. Thomas L. Shipman, Los Alamos, along with local participants.

Each day will be devoted to a separate subject: Wednesday, the pelvis; Thursday, the joints; Friday, the adrenals. A one-hour closed circuit television program will be presented each morning, originating from Denver General Hospital. There will also be sports events, a stag dinner and smoker on Tuesday evening, and a dinner dance on Thursday evening.

A postgraduate symposium on pulmonary diseases will be held in the Post Theater of Fitzsimons Army Hospital in Denver, September 26-30, under the sponsorship of the hospital, the University of Colorado School of Medicine, and the American Trudeau Society. Dr. Michael L. Furcolow, of the University of Kansas School of Medicine, and Major Paul W. Schafer will be guest clinicians. The course is open to all physicians for a fee of $5.00, but registration will be limited to 300.

Programs may be secured from Director of Postgraduate Medical Education, 4200 East Ninth Avenue, Denver 20, Colorado.

A course in occupational skin problems will be presented at the Kettering Laboratory, Cincinnati, October 10-14, by the University of Cincinnati and the Public Health Service. The registration fee will be $75. Applications for registration should be sent to the Institute of Industrial Health, Kettering Laboratory, Eden and Bethesda, Cincinnati 19, Ohio.

The American Goiter Association again offers the Van Meter prize award of $300 and two honorable mentions for the best essays submitted covering original work on problems related to the thyroid gland. Deadline for entries is January 1, 1956. Information may be secured from the secretary, Dr. John C. McClintock, 149½ Washington Avenue, Albany, New York.

The 24th venereal disease postgraduate course for physicians, sponsored by the University of Chicago and the Public Health Service, will be given at the University of Chicago, September 26-30. No tuition will be charged. Applications for admission are to be sent to the Section of Dermatology, Department of Medicine, University of Chicago, Chicago 37, Illinois.

The Academy of Psychosomatic Medicine will hold its second annual meeting, October 6-8, at the Plaza Hotel, New York City. The subject of the program is "The Psychosomatic Aspects of Drug Administration." No registration fee will be charged. Programs may be obtained from the secretary, Dr. Ethan Allan Brown, 75 Bay State Road, Boston.

A postgraduate course on fractures and joint injuries will be given at the University of Colorado School of Medicine, October 20-22. All physicians are invited to attend, and the program will be intended for the general physician. Information may be obtained from Director of Postgraduate Education, 4200 East Ninth Avenue, Denver 20, Colorado.

The American College of Physicians announces that a course entitled "Recent Developments in Psychiatry for the Internist" will be presented at the Menninger School of Psychiatry, October 24-28. Cooperating in the program are the Menninger School of Psychiatry, Topeka State Hospital, Winter VA Hospital, and the University of Kansas School of Medicine. Dr. Karl A. Menninger is director. Members of the College will pay a registration fee of $30 and non-members $60. Registration is limited to 100. Registrations are to be made through E. R. Loveland, M.D., 4200 Pine Street, Philadelphia 4, Pennsylvania.

The annual convention of the American College of Gastroenterology will be held at the Shoreland, Chicago, October 24-26. The program will include a panel discussion on peptic ulcer. The annual course in postgraduate gastroenterology will follow, October 27-29, also at the Shoreland. Information may be obtained from the College, 33 West 60th Street, New York 23, New York.

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To Head Department of Pharmacology

Dr. Lawrence Peters joined the faculty of the University of Kansas School of Medicine on July 1 as professor and chairman of the department of pharmacology, leaving a similar position he had held in the Tulane University School of Medicine, New Orleans, since 1953.

A teacher in the various schools in which he has studied since 1938, Dr. Peters has done extensive research on basic studies on the kidney as well as on treatments for threadworm and flat worm infections. Dr. Peters, a native of Canada, has been a citizen of this country since 1950.

Television Shows of Medical Interest

The fall schedule for two network medical television programs produced with the cooperation of the American Medical Association will be started in September. One series is produced by Ciba Pharmaceutical Products and the other by Smith, Kline and French Laboratories.

The Ciba program, *Medical Horizons,* on ABC-TV, will be presented weekly on Monday evenings at 8:30. It will depict specific accomplishments in the field of medicine as exemplified by the teamwork of modern medical research, education, and practice. The telecasts will originate in medical institutions and research centers throughout the country.

Smith, Kline and French will present six programs in its 1955-1956 series, continuing under the *March of Medicine* title. The first will be on Tuesday, September 20, at 8:30 over the NBC-TV network.

Standards for Grievance Committees

Standards for medical society grievance or mediation committees are being developed by a special committee appointed by the A.M.A.'s Board of Trustees. The group of consultants includes the executive secretaries of three state societies and several A.M.A. staff members. They will visit 25 state association offices to collect information and will assemble data from the others by correspondence.

In addition, a special survey form is being sent to approximately 70 county societies. Some of those will be visited by the committee to gain information on a variety of types of grievance organizations.

Mr. J. W. Holloway, Jr., who has been on the legal staff of the American Medical Association almost 30 years, has announced his retirement. He will continue, however, as a member of the A.M.A. Committee on Medicolegal Problems.

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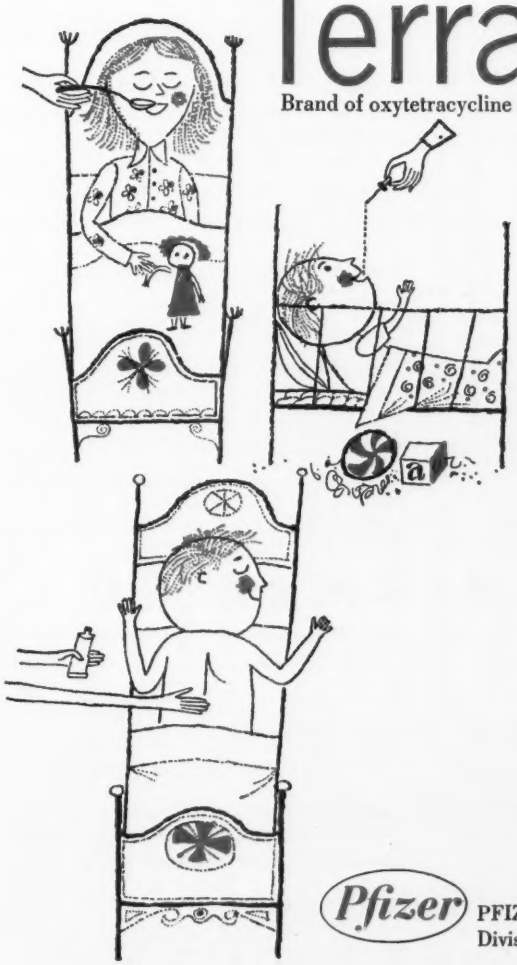

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*Farley, W. J.: Oxytetracycline in Pediatrics, Internat. Rec. Med. *168*:140 (March) 1955.

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The Children's Bureau reports that 24,000 mothers would die in childbearing this year if 1935 mortality rates still held. Instead, some 2,000 may lose their lives. Also, under the present mortality rate, some 100,000 infants under one year of age may die this year, but the rate in 1935 would cause the deaths of 230,000.

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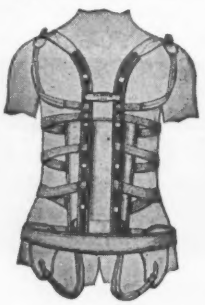

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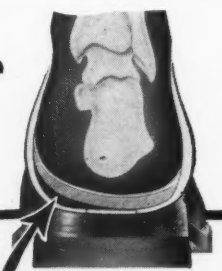

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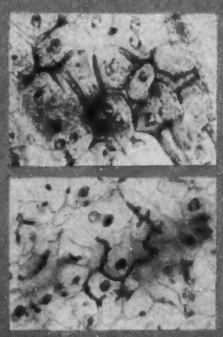

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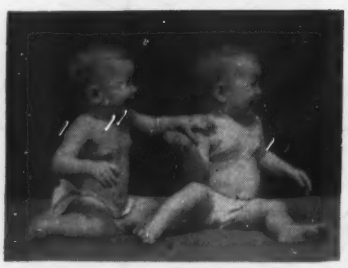

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(1) Jeans, P. C., in A. M. A. Handbook of Nutrition, ed. 2, Philadelphia, Blakiston, 1951, pp. 275-278.

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